A 27-year-old man comes to the office due to cough, chest discomfort, and dyspnea on exertion. Symptoms began approximately a month ago and were initially mild but have gradually worsened. He has also lost 4.5 kg (10 lb) over the past 2 months. The patient has no chronic medical conditions. He smokes a pack of cigarettes a day and drinks an average of 4 beers each weekend. The patient does not use illegal drugs and has not had multiple sexual partners. Physical examination is unremarkable. Chest imaging reveals a large, anterior mediastinal mass. Subsequent blood work shows elevated levels of β-hCG and alpha fetoprotein. Which of the following is the most likely diagnosis?

A. Benign teratoma
B. Bronchogenic cyst
C. Hodgkin lymphoma
D. Nonseminomatous germ cell tumor
E. Seminoma
F. Thymoma

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A. ~~Benign teratoma~~ (8%)

B. ~~Bronchogenic cyst~~ (1%)

C. ~~Hodgkin lymphoma~~ (4%)

✓ D. Nonseminomatous germ cell tumor (59%)

E. Seminoma (13%)

F. ~~Thymoma~~ (13%)

Correct

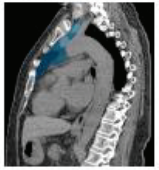
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Mediastinal Compartments, Structures, & Masses

Compartment	Structures	Masses
Anterior 	• Thymus • Lymph nodes*	• Thymic neoplasms (eg, thymoma) • Lymphoma • Germ cell tumors • Teratomas • Seminomas, nonseminomas • Thyroid tissue (eg, ectopic, substernal goiter)
Middle** 	• Lymph nodes* • Pericardium • Heart & great vessels • Trachea & main bronchi • Esophagus	• Lymphadenopathy (eg, sarcoidosis, lung cancer), lymphoma • Benign cystic masses (eg, pericardial cyst, bronchogenic cyst) • Vascular masses • Esophageal tumors
Posterior** 	• Neural tissue • Vertebrae • Lymph nodes*	• Neurogenic tumors (eg, schwannoma, neurofibroma), meningocele • Spinal masses (eg, metastases) • Lymphoma

*Lymph nodes, from which lymphoma may arise, are present in all 3 compartments

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*Lymph nodes, from which lymphoma may arise, are present in all 3 compartments.
**Some sources define the middle & posterior compartments based on their relationship to the posterior pericardial surface rather than the posterior thoracic wall.

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Masses that arise within the mediastinum are typically classified according to their compartment. Within the **anterior mediastinum**, the most common etiologies are the **4 Ts**: thymoma, teratoma (and other **germ cell tumors [GCTs]**), "terrible" lymphoma, and thyroid neoplasm. This patient with a large, anterior mediastinal mass and elevated **β-hCG** and **alpha fetoprotein** (AFP) levels most likely has a GCT.

In adults, the anterior mediastinum is the most common location for extragonadal GCTs, which may be either benign (eg, benign teratoma) or malignant (eg, seminomas, nonseminomatous GCTs). These occur predominantly in young men and can cause chest discomfort and compressive symptoms (eg, cough, dyspnea) due to mass effect on adjacent structures (eg, trachea). GCT type can usually be distinguished by differences in serum tumor markers:

- Seminomas may cause elevated β-hCG levels in a minority of cases, but AFP is almost always normal **(Choice E)**.
- **Nonseminomatous GCTs** (eg, yolk sac tumor, choriocarcinoma, embryonal carcinoma) cause **elevated AFP and/or β-HCG** in the majority (~85%) of patients.

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- **Nonseminomatous GCTs** (eg, yolk sac tumor, choriocarcinoma, embryonal carcinoma) cause **elevated AFP and/or β-HCG** in the majority (~85%) of patients.
- Teratomas that are benign (vs malignant) do not typically produce elevated AFP or β-HCG **(Choice A)**.

(Choice B) Bronchogenic cysts, congenital cysts that arise due to abnormal development of the bronchopulmonary foregut, are an uncommon cause of mediastinal mass; they are typically located in the middle (vs the anterior) mediastinum and do not cause elevated AFP and β-hCG levels.

(Choice C) Lymphomas, including Hodgkin lymphoma, can arise in any of the mediastinal compartments, including the anterior mediastinum. They can cause weight loss but classically produce additional systemic symptoms (eg, fever, night sweats); they do not cause elevated AFP and β-hCG levels.

(Choice F) Thymomas are a common cause of anterior mediastinal mass. However, they do not cause elevated AFP and β-hCG levels, and they are often associated with paraneoplastic syndromes (eg, myasthenia gravis).

Educational objective:
The most common masses in the anterior mediastinum are the 4 Ts: thymoma, teratoma (and other germ cell tumors), "terrible" lymphoma, and thyroid neoplasm. An anterior mediastinal mass with elevated serum

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(Choice B) Bronchogenic cysts, congenital cysts that arise due to abnormal development of the bronchopulmonary foregut, are an uncommon cause of mediastinal mass; they are typically located in the middle (vs the anterior) mediastinum and do not cause elevated AFP and β-hCG levels.

(Choice C) Lymphomas, including Hodgkin lymphoma, can arise in any of the mediastinal compartments, including the anterior mediastinum. They can cause weight loss but classically produce additional systemic symptoms (eg, fever, night sweats); they do not cause elevated AFP and β-hCG levels.

(Choice F) Thymomas are a common cause of anterior mediastinal mass. However, they do not cause elevated AFP and β-hCG levels, and they are often associated with paraneoplastic syndromes (eg, myasthenia gravis).

Educational objective:
The most common masses in the anterior mediastinum are the 4 Ts: thymoma, teratoma (and other germ cell tumors), "terrible" lymphoma, and thyroid neoplasm. An anterior mediastinal mass with elevated serum levels of alpha fetoprotein and β-hCG is classic for a nonseminomatous germ cell tumor.

Pathology	Hematology & Oncology	Mediastinal masses
Subject	System	Topic

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A mutation in a non-coding DNA sequence is believed to affect expression of the gene coding for a specific fetal enzyme. Liver and bone marrow cells from the fetus and his parents are obtained. Which of the following is the best method to determine if this gene is being transcribed in cultures of the isolated cells?

A. Northern blot
B. Western blot
C. Southern blot
D. Southwestern blot
E. Enzyme-linked immunosorbent assay

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A mutation in a non-coding DNA sequence is believed to affect expression of the gene coding for a specific fetal enzyme. Liver and bone marrow cells from the fetus and his parents are obtained. Which of the following is the best method to determine if this gene is being transcribed in cultures of the isolated cells?

- ✓ A. Northern blot (50%)
- B. Western blot (12%)
- ✗ C. Southern blot (25%)
- D. Southwestern blot (7%)
- E. Enzyme-linked immunosorbent assay (4%)

Incorrect
Correct answer
A

50%
Answered correctly

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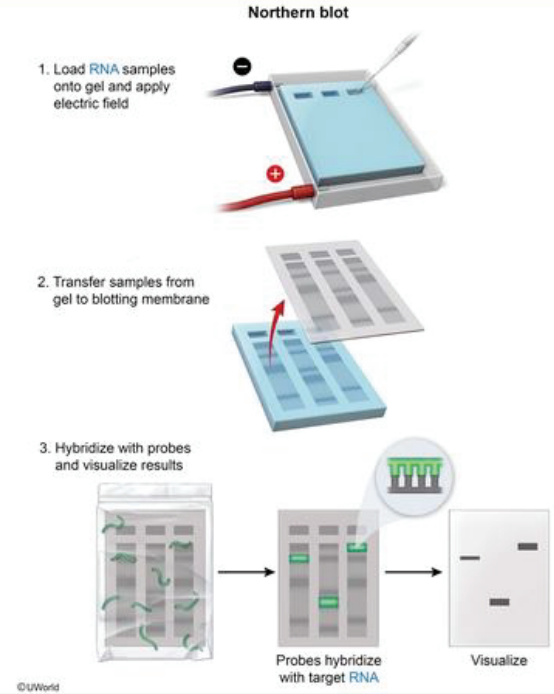
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Explanation

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with target RNA

The Southern, Western, Northern and Southwestern blot procedures are techniques used to analyze and identify DNA fragments, proteins, mRNA, and DNA-bound proteins, respectively. The best method for determining whether a gene is undergoing **transcription** is to analyze for the presence of its **mRNA** using a **Northern blot**. In the case described above, Northern blot analysis of each of the cell culture samples can determine if mRNA corresponding to the gene of interest is being transcribed.

All of the "blot" tests rely on the same basic techniques. First, the components of the unknown sample – DNA for Southern blots, mRNA for Northern blots, protein for Western blots, and DNA-bound protein for Southwestern blots – are separated by size and charge via gel electrophoresis. The resultant bands are then blotted onto a nitrocellulose membrane and incubated with a labeled hybridization probe or antibody to identify the specific DNA fragment, mRNA molecule or protein of interest.

(Choice B) A complete failure of gene expression would lead to a failure to produce the protein, which can be detected by Western blotting. However, the question is asking how to determine if the gene is being transcribed (genes may be transcribed but not properly expressed if there is a problem with protein translation). As transcription refers to the production of mRNA from a DNA template, a test that detects specific mRNA sequences (Northern blot) would be most appropriate.

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translation). As transcription refers to the production of mRNA from a DNA template, a test that detects specific mRNA sequences (Northern blot) would be most appropriate.

(Choices C and D) This patient's mutation in a non-coding DNA sequence (likely affecting a promotor or enhancer region) is resulting in decreased gene expression. A Southern or Southwestern blot could potentially be used to detect the mutated DNA sequence and assess for transcription factor binding. However, the degree of transcription of the affected gene is better assessed through direct detection of its associated mRNA.

(Choice E) The ELISA (enzyme-linked immunosorbent assay) is a test commonly employed to measure the amount of a protein in body fluids. It can be quantitative, for example, to measure plasma insulin levels.

Educational objective:
Northern blots detect target mRNA in a sample and can be used to assess the degree of gene transcription.

Genetics	Biochemistry (General Principles)	Transcription
Subject	System	Topic

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Biochemists working for a national endocrinology institute are investigating the specifics underlying glucose transport across adipose cell membranes. One of their experiments shows that, in the presence of insulin, D-glucose transport across the plasma membrane of adipocytes is much faster than L-glucose transport. Which of the following transport processes best describes the mechanism for glucose entry into these cells?

A. Simple diffusion
B. Receptor-mediated endocytosis
C. Carrier-mediated transport
D. Primary active transport
E. Co-transport

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Biochemists working for a national endocrinology institute are investigating the specifics underlying glucose transport across adipose cell membranes. One of their experiments shows that, in the presence of insulin, D-glucose transport across the plasma membrane of adipocytes is much faster than L-glucose transport. Which of the following transport processes best describes the mechanism for glucose entry into these cells?

A. Simple diffusion (4%)
B. Receptor-mediated endocytosis (16%)
✓ C. Carrier-mediated transport (60%)
D. Primary active transport (7%)
E. Co-transport (10%)

Correct

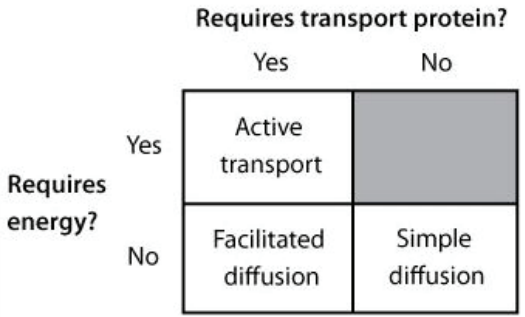
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Classification of transport across cell membranes



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Glucose is the major source of energy for all cells of the body. In the majority of tissues, glucose transport occurs along its concentration gradient, from higher concentrations outside the cell toward lower concentrations inside the cell. However, glucose cannot passively diffuse across the cell membrane in any significant amount and requires carrier proteins to aid its crossing. Transport across the cell membrane by carrier proteins (which undergo conformational changes as the substrate is transported, unlike channel proteins) is termed carrier-mediated transport. Transport that is facilitated by transmembrane proteins without the expenditure of energy is called **facilitated diffusion**.

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without the expenditure of energy is called **facilitated diffusion**.

Transmembrane carrier proteins that belong to the GLUT family transport glucose by facilitated diffusion. These proteins are stereoselective and preferentially catalyze the entrance of D-glucose rather than L-glucose into cells. **GLUT4** is the insulin-sensitive transporter found in skeletal muscle cells and adipocytes. In these cells, the GLUT4 protein is stored in cytoplasmic vesicles. Under the influence of insulin, the transporter protein is incorporated into the cell membrane. An increased number of transporters in the membrane leads to an increased rate of glucose uptake by the cells. Another important glucose transporter is **GLUT2**. It facilitates export of glucose from the liver, small intestine, and kidneys into the circulation and also helps to control insulin secretion in the pancreas.

(Choice A) Simple diffusion refers to the movement of particles along their concentration gradient directly through the cell membrane. Transport of gases (O_2 and CO_2) occurs via simple diffusion, as the membrane is very permeable to small, nonpolar molecules.

(Choice B) Endocytosis allows for cellular uptake through the formation of membrane-bound, typically clathrin-coated, vesicles. Uptake of cholesterol by cells occurs by means of receptor-mediated endocytosis (mediated by the LDL receptor).

(Choices D and E) Active transport refers to the movement of a substance against its concentration

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is very permeable to small, nonpolar molecules.

(Choice B) Endocytosis allows for cellular uptake through the formation of membrane-bound, typically clathrin-coated, vesicles. Uptake of cholesterol by cells occurs by means of receptor-mediated endocytosis (mediated by the LDL receptor).

(Choices D and E) Active transport refers to the movement of a substance against its concentration gradient. This process requires energy as well as transport proteins. In primary active transport, the energy required for transport against the concentration gradient is provided by the hydrolysis of ATP. In secondary active transport, this energy is generated by co-transport of a separate substance down its concentration gradient. Transport of glucose against the concentration gradient occurs via the Na/glucose symporter, which is found in the intestinal and renal tubular epithelium and is used to transfer glucose intracellularly from the lumen.

Educational objective:
Transport of glucose into the cells of most tissues occurs by means of facilitated diffusion. Glucose moves from areas of high concentration to areas of low concentration with the help of transmembrane glucose transporter proteins (GLUT). These carrier proteins are stereoselective and have preference for D-glucose.

Biochemistry Biochemistry (General Principles) Cellular transports

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A 6-month-old boy is brought to the emergency department by his mother because of recent onset of vomiting, irritability, and jaundice. The infant was born at term and had been healthy until the onset of these symptoms. All of his vaccinations are up-to-date. He had been breast-fed exclusively until 1 week ago, when cereals and fruit juices were introduced into his diet. Further evaluation reveals hepatomegaly and abnormal liver function tests. Which of the following enzymes is most likely to be deficient in this patient?

A. Galactose-1-phosphate uridyl transferase
B. Aldolase B
C. Fructokinase
D. Galactokinase
E. Acid α-glucosidase

Submit

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A. Galactose-1-phosphate uridyl transferase (9%)
B. Aldolase B (64%)
C. Fructokinase (20%)
D. Galactokinase (3%)
E. Acid α-glucosidase (2%)

Correct

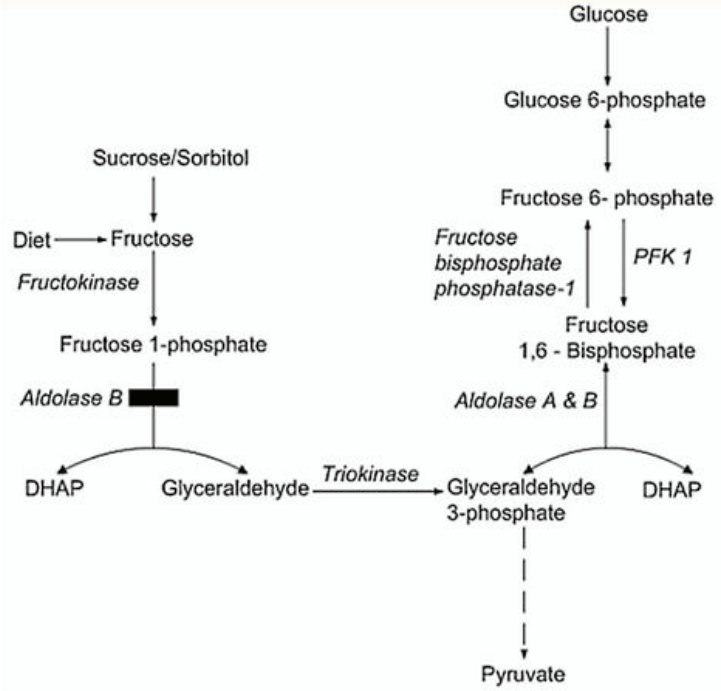
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Pyruvate

Dietary fructose is obtained mainly from fruits, vegetables, honey, table sugar (sucrose), and processed foods. Fructose is rapidly absorbed in the proximal small bowel by the hexose transporter GLUT 5. Initial metabolism of fructose involves three enzymes: fructokinase, aldolase B, and triokinase. Fructose is phosphorylated on the first carbon by hepatic fructokinase, yielding fructose-1-phosphate. Metabolism of fructose-1-phosphate by aldolase B generates dihydroxyacetone phosphate (DHAP) and glyceraldehyde. Glyceraldehyde is then phosphorylated to glyceraldehyde-3-phosphate (G3P), an intermediate of glycolysis, by triose kinase. DHAP can also be converted to G3P by triose phosphate isomerase.

Aldolase B deficiency causes the potentially life-threatening disorder known as hereditary fructose intolerance. Patients typically present when fructose-containing foods are introduced into the diet. The primary manifestations are vomiting and hypoglycemia about 20-30 minutes after fructose ingestion. Hypoglycemia results from intracellular accumulation of fructose-1-phosphate and depletion of inorganic phosphate, which inhibit glycogenolysis and gluconeogenesis. Failure to thrive, hepatomegaly, and jaundice can also occur. Undiagnosed individuals may eventually develop liver and renal failure. Elimination of dietary fructose is the mainstay of treatment and results in symptom improvement with a good long-term prognosis.

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(Choices A and D) Galactose-1-phosphate uridyl transferase deficiency (classic galactosemia) is an autosomal recessive disorder characterized by vomiting, feeding intolerance, neonatal jaundice, hepatomegaly, and death if untreated. Symptoms start soon after breastfeeding is initiated. Galactokinase deficiency is a more benign disorder of galactose metabolism that results in the formation of neonatal cataracts.

(Choice C) Fructokinase deficiency causes essential fructosuria, a benign autosomal recessive disorder. Fructose from the diet is absorbed and secreted freely in the urine due to impairment of the first step in fructose metabolism.

(Choice E) Glycogenolysis is accomplished mainly by glycogen phosphorylase and debranching enzyme, but a small amount is also broken down by the lysosomal enzyme α-1,4-glucosidase. Alpha-glucosidase (or acid maltase) deficiency causes Pompe disease. This disease presents not with hypoglycemia, but with cardiomyopathy and hypotonia.

Educational objective:
Aldolase B deficiency causes hereditary fructose intolerance. This disease manifests after introduction of fructose into the diet with vomiting and hypoglycemia about 20-30 minutes after fructose ingestion. These infants can present with failure to thrive, jaundice, and hepatomegaly

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Educational objective:
Aldolase B deficiency causes hereditary fructose intolerance. This disease manifests after introduction of fructose into the diet with vomiting and hypoglycemia about 20-30 minutes after fructose ingestion. These infants can present with failure to thrive, jaundice, and hepatomegaly.

Biochemistry	Biochemistry (General Principles)	Fructose metabolism
Subject	System	Topic

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A 35-year-old man comes to the office with progressively worsening fatigue associated with dark urine and back pain. Two days ago, the patient ate some large, flat beans brought home by his wife after a business trip to Egypt. Physical examination shows jaundice and pallor. Laboratory results reveal a hemoglobin level of 8 g/dL. Further evaluation reveals deficiency of an enzyme involved in the conversion of glucose-6-phosphate to ribulose-5-phosphate. The substance generated during this conversion is necessary for which of the following biochemical processes?

A. ADP phosphorylation
B. Fatty acid synthesis
C. Glycogen storage
D. Ketone body synthesis
E. Protein degradation

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- A. ADP phosphorylation (29%)
- ✓ B. Fatty acid synthesis (44%)
- C. Glycogen storage (9%)
- D. Ketone body synthesis (8%)
- E. Protein degradation (8%)

Correct

44% Answered correctly

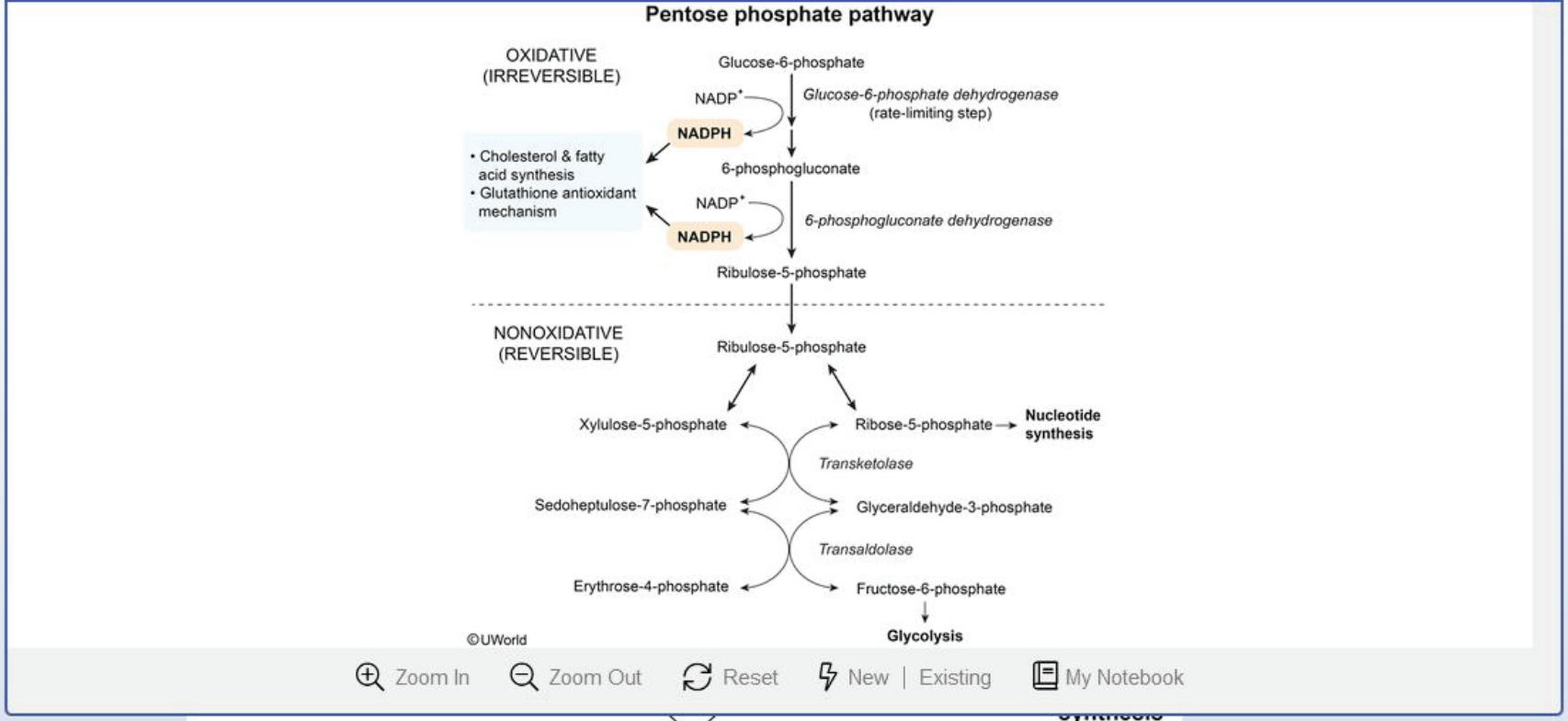
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Glycolysis

This patient most likely has **glucose-6-phosphate dehydrogenase (G6PD) deficiency**. G6PD catalyzes the first step in the pentose phosphate pathway (PPP), the oxidative portion of which generates 2 molecules of NADPH while converting glucose-6-phosphate to ribulose-5-phosphate. The nonoxidative reactions of the PPP reversibly convert ribulose-5-phosphate into ribose-5-phosphate (substrate for nucleotide synthesis) or glycolytic intermediates that can be used for energy production.

Because the PPP is the **main source of NADPH**, the pathway is particularly active in:

- Cells experiencing **high oxidative stress** (eg, erythrocytes) in which NADPH is used to regenerate reduced glutathione, an antioxidant that helps maintain cell integrity
- Organs such as the liver and adrenal cortex that are involved in **reductive biosynthesis** (eg, synthesis of fatty acids, cholesterol, steroids) and cytochrome P450 metabolism
- Phagocytic cells generating a respiratory burst via NADPH oxidase

In patients with G6PD deficiency, erythrocytes are unable to maintain a sufficient supply of reduced glutathione during periods of increased oxidative stress, which can occur with certain infections (eg, pneumonia, viral hepatitis), consumption of fava beans, or specific medications (eg, primaquine, sulfa

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pneumonia, viral hepatitis), consumption of fava beans, or specific medications (eg, primaquine, sulfa drugs). The resulting oxidative damage causes **acute hemolytic anemia** and jaundice.

(Choice A) NADH can be used as a reducing agent to convert ADP to ATP during oxidative phosphorylation. In contrast to NADH, NADPH cannot be used to convert ADP into ATP.

(Choice C) Glycogenesis is the process by which glucose is stored for later use through the addition of glucose molecules to glycogen chains. It does not require NADPH.

(Choice D) Ketone bodies are formed mainly in the liver during times of fasting when there is increased fat degradation. Cytosolic HMG-CoA synthase is the starting point of cholesterol synthesis whereas the mitochondrial version of the enzyme is the rate-limiting step in ketone body synthesis. Unlike cholesterol synthesis, ketone body production does not require NADPH.

(Choice E) Protein catabolism begins with the hydrolysis of polypeptides into amino acids. These subsequently undergo transamination reactions that funnel the amine nitrogen predominately into glutamate, which is oxidatively deaminated to produce ammonia. The urea cycle then converts ammonia into urea for elimination in the urine.

Educational objective:

Glucose-6-phosphate dehydrogenase is the rate-limiting enzyme in the pentose phosphate pathway, the

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(Choice D) Ketone bodies are formed mainly in the liver during times of fasting when there is increased fat degradation. Cytosolic HMG-CoA synthase is the starting point of cholesterol synthesis whereas the mitochondrial version of the enzyme is the rate-limiting step in ketone body synthesis. Unlike cholesterol synthesis, ketone body production does not require NADPH.

(Choice E) Protein catabolism begins with the hydrolysis of polypeptides into amino acids. These subsequently undergo transamination reactions that funnel the amine nitrogen predominately into glutamate, which is oxidatively deaminated to produce ammonia. The urea cycle then converts ammonia into urea for elimination in the urine.

Educational objective:
Glucose-6-phosphate dehydrogenase is the rate-limiting enzyme in the pentose phosphate pathway, the major source of cellular NADPH. This molecule is necessary for reducing glutathione (protects red blood cells from oxidative damage) and for the biosynthesis of cholesterol, fatty acids, and steroids.

Biochemistry	Biochemistry (General Principles)	Hyperphosphatemia
Subject	System	Topic

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A 27-year-old man is brought to the emergency department due to confusion. His roommate says that he has been binge drinking for the last 5 days and probably has had very little to eat. The patient's medical history is significant for alcohol-related seizures 1 year ago. He had been sober until 2 weeks ago, when he started drinking again. The patient's past medical history is otherwise unremarkable. On examination, he responds to voice but does not follow commands. Fingerstick glucose is 35 mg/dL and urine is strongly positive for ketones. Suppression of which of the following is the primary cause of this patient's hypoglycemia?

A. Gluconeogenesis
B. Glycogenolysis
C. Insulin clearance
D. Insulin sensitivity
E. Lipolysis

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- ✓ A. Gluconeogenesis (73%)
- B. Glycogenolysis (13%)
- C. Insulin clearance (2%)
- ✗ D. Insulin sensitivity (4%)
- E. Lipolysis (6%)

Incorrect

73%

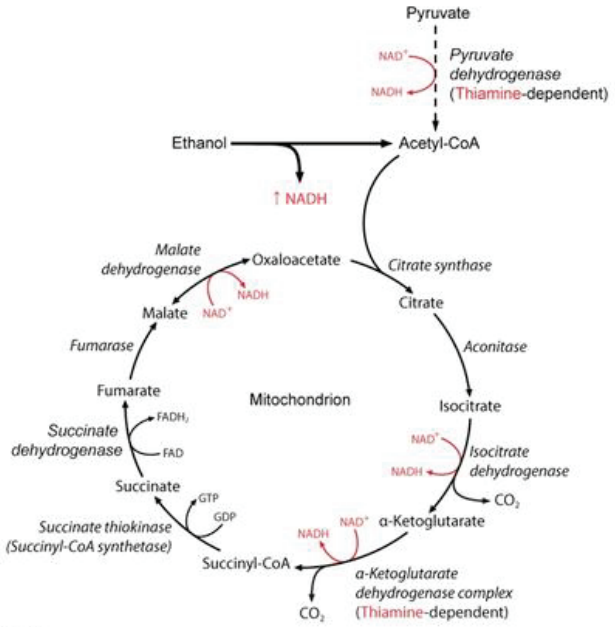
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Inhibition of the citric acid cycle by ethanol



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The metabolism of **ethanol** by alcohol dehydrogenase and aldehyde dehydrogenase reduces NAD^+ to NADH and increases the **NADH/NAD^+ ratio**. This inhibits all other pathways requiring NAD^+, including reactions required for gluconeogenesis. In particular, lactate cannot be converted to pyruvate, and instead the reaction is driven from pyruvate toward lactate. In addition, excess NADH inhibits the conversion of malate to oxaloacetate. Pyruvate and oxaloacetate are intermediates in gluconeogenesis; therefore, conversion of these molecules to lactate and malate **inhibits gluconeogenesis**.

Alcohol does not inhibit glycogenolysis **(Choice B)**, and so in the initial phase of binge drinking (heavy alcohol intake with reduced nutritional carbohydrate intake), hepatic glycogenolysis is able to maintain euglycemia. However, after a prolonged binge, hepatic glycogen is eventually depleted and blood glucose levels drop.

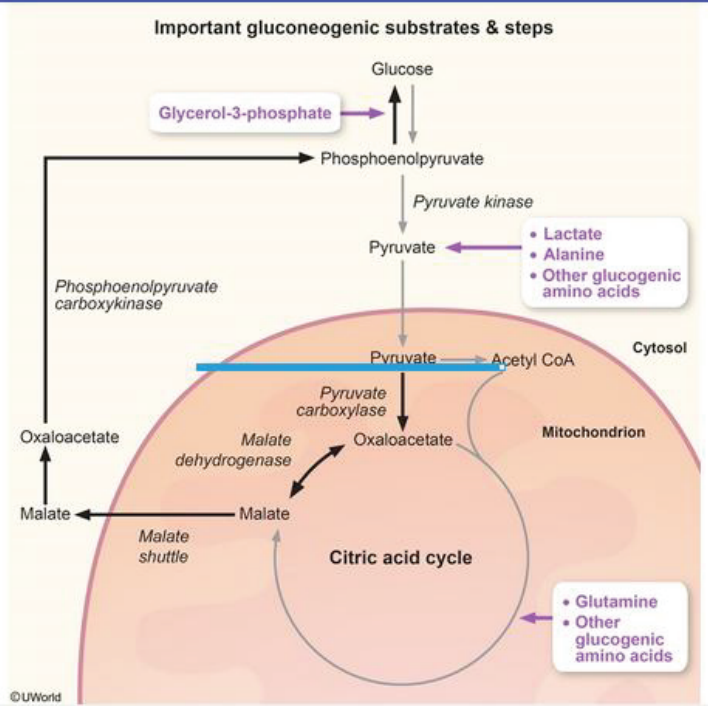
(Choices C and D) Ethanol has no direct effect on insulin sensitivity. Impaired clearance of insulin is a major contributor to hypoglycemia in patients with advanced renal insufficiency.

(Choice E) Excess NADH inhibits free fatty acid oxidation, thereby diverting free fatty acids away from lipolysis to the formation of triglycerides. This contributes to hepatic steatosis in alcoholic patients but does not cause hypoglycemia.

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alcohol intake with reduced nutritional carbohydrate intake), hepatic glycogenolysis is able to maintain euglycemia. However, after a prolonged binge, hepatic glycogen is eventually depleted and blood glucose levels drop.

(Choices C and D) Ethanol has no direct effect on insulin sensitivity. Impaired clearance of insulin is a major contributor to hypoglycemia in patients with advanced renal insufficiency.

(Choice E) Excess NADH inhibits free fatty acid oxidation, thereby diverting free fatty acids away from lipolysis to the formation of triglycerides. This contributes to hepatic steatosis in alcoholic patients but does not cause hypoglycemia.

Educational objective:

Ethanol inhibits gluconeogenesis and can cause hypoglycemia once hepatic glycogen stores are depleted.

References

- Case of alcoholic ketoacidosis accompanied with severe hypoglycemia.

Biochemistry	Biochemistry (General Principles)	Gluconeogenesis
Subject	System	Topic

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A 2-year-old boy is evaluated for easy bruising. His parents report that he develops marked bruising and open wounds following minor trauma. The skin is difficult to suture due to its extreme fragility. Physical examination reveals hyperextensible skin, multiple ecchymoses over the forearms and pretibial regions, and an umbilical hernia. A skin biopsy is performed, and histochemical evaluation of the biopsy reveals a defect in extracellular processing of collagen. Which of the following steps of collagen synthesis is most likely impaired in this patient?

A. Glycosylation of hydroxylysine residues
B. Interchain C-terminal disulfide bond formation
C. N-terminal propeptide removal
D. Proline residue hydroxylation
E. Triple helix formation

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A 2-year-old boy is evaluated for easy bruising. His parents report that he develops marked bruising and open wounds following minor trauma. The skin is difficult to suture due to its extreme fragility. Physical examination reveals hyperextensible skin, multiple ecchymoses over the forearms and pretibial regions, and an umbilical hernia. A skin biopsy is performed, and histochemical evaluation of the biopsy reveals a defect in extracellular processing of collagen. Which of the following steps of collagen synthesis is most likely impaired in this patient?

A. Glycosylation of hydroxylysine residues (10%)
B. Interchain C-terminal disulfide bond formation (18%)
C. N-terminal propeptide removal (23%)
D. Proline residue hydroxylation (17%)
E. Triple helix formation (29%)

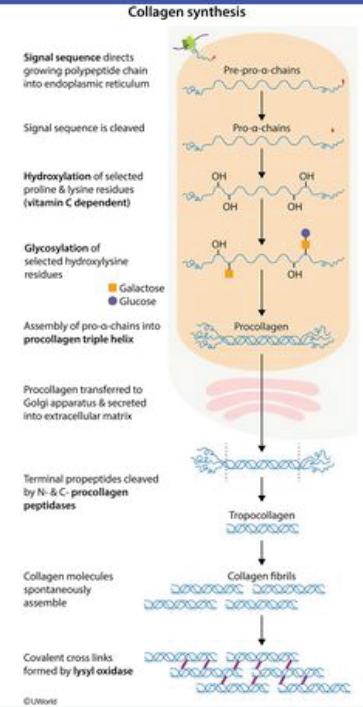
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This child likely has **Ehlers-Danlos syndrome**, a group of rare hereditary disorders characterized by **defective collagen synthesis**. The condition can be caused by a **deficiency** in **procollagen peptidase**, the enzyme that cleaves terminal propeptides from procollagen in the extracellular space. Impaired propeptide removal results in the formation of soluble collagen that does not properly crosslink. Consequently, patients often have joint laxity, **hyperextensible skin, fragile tissue** with easy bruising, and poor wound healing.

Each collagen molecule consists of 3 polypeptide α-chains held together by hydrogen bonds, forming a triple helix. Collagen assumes this conformation because each of the α-chains has a simple, repetitive amino acid sequence represented as $(Gly\text{-}X\text{-}Y)_n$. The smallest amino acid, glycine (Gly), is necessary at every third position to ensure compact coiling of the helix. Many of the amino acids represented by X and Y are proline residues, which kink the polypeptide chain and enhance the rigidity of the helical structure due to their ring configuration.

Mature collagen is synthesized by fibroblasts, osteoblasts, and chondroblasts through the following steps:

1. As translation begins in the cytoplasm, an amino acid signal sequence at the N-terminus of the α-chain facilitates ribosomal binding to the rough endoplasmic reticulum (RER) and passage of the growing polypeptide chain (pre-pro-α-chain) into the RER.

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polypeptide chain (pre-pro-α-chain) into the RER.

2. Inside the RER, the hydrophobic signal sequence is cleaved to yield the pro-α-chain. Proline and lysine at the Y positions of the pro-α-chain are hydroxylated to hydroxyproline and hydroxylysine, respectively **(Choice D)**. Glycosylation of select hydroxylysine residues also occurs within the RER **(Choice A)**.

3. The central helical region of the pro-α-chain is flanked by N- and C-terminal propeptides. Disulfide bond formation between the C-terminal propeptide region of 3 α-chains brings the chains into an alignment favorable for assembly into a triple helix (procollagen molecule) **(Choices B and E)**.

4. Procollagen molecules are then transported through the Golgi apparatus into the extracellular space. The N- and C-terminal propeptides are cleaved by procollagen peptidases, converting procollagen into less soluble tropocollagen.

5. Tropocollagen monomers self-assemble into collagen fibrils. Finally, lysyl oxidase helps create covalent crosslinks between collagen fibrils to form strong collagen fibers.

Educational objective:

Ehlers-Danlos syndrome is a group of rare hereditary disorders characterized by defective collagen synthesis. It can be caused by procollagen peptidase deficiency, which results in impaired cleavage of

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(Choice A).

3. The central helical region of the pro-α-chain is flanked by N- and C-terminal propeptides. Disulfide bond formation between the C-terminal propeptide region of 3 α-chains brings the chains into an alignment favorable for assembly into a triple helix (procollagen molecule) **(Choices B and E)**.

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5. Tropocollagen monomers self-assemble into collagen fibrils. Finally, lysyl oxidase helps create covalent crosslinks between collagen fibrils to form strong collagen fibers.

Educational objective:

Ehlers-Danlos syndrome is a group of rare hereditary disorders characterized by defective collagen synthesis. It can be caused by procollagen peptidase deficiency, which results in impaired cleavage of terminal propeptides in the extracellular space. Patients often have joint laxity, hyperextensible skin, and tissue fragility due to the formation of soluble collagen that does not properly crosslink.

References

- Defect in conversion of procollagen to collagen in a form of Ehlers-Danlos syndrome

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A 5-year-old girl is brought to the clinic due to several months of fatigue and difficulty walking. She ambulates normally at first but rapidly becomes weak and tired. The patient has not been ill recently and is usually happy and playful. She has a history of mild motor delays but is otherwise developmentally normal. Vital signs are within normal limits. Examination shows mildly decreased power in all extremities but no ataxia. Cardiac auscultation reveals a 1/6 systolic murmur and an S3 gallop. Laboratory results are as follows:

Serum chemistry	
Glucose	37 mg/dL
Creatine kinase	304 U/L
Urinalysis	
Protein	none
Glucose	negative
Ketones	negative

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Protein	none
Glucose	negative
Ketones	negative
Leukocyte esterase	negative
Nitrites	negative

Muscle biopsy shows a very low carnitine content. This patient most likely has deficient synthesis of which of the following substances?

A. Acetoacetate
B. Arachidonic acid
C. Glutathione
D. Homocysteine
E. Lactate
F. Palmitate

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Ketones	negative
Leukocyte esterase	negative
Nitrites	negative

Muscle biopsy shows a very low carnitine content. This patient most likely has deficient synthesis of which of the following substances?

- A. Acetoacetate (44%)
- B. Arachidonic acid (3%)
- C. Glutathione (6%)
- D. Homocysteine (8%)
- E. Lactate (8%)
- F. Palmitate (27%)

Correct

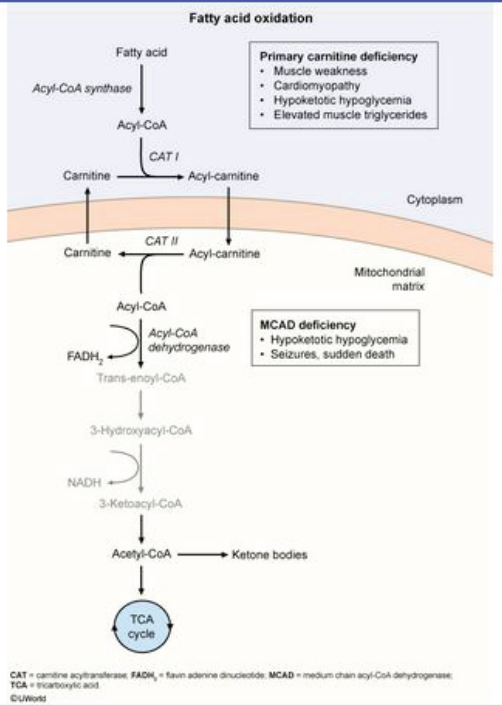
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TCA = tricarboxylic acid.

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This patient's myopathy (eg, elevated creatine kinase, weakness), cardiomyopathy (eg, S3 gallop), and **hypoketotic hypoglycemia** (eg, absence of ketones in the urine) in the setting of **decreased muscle carnitine** content is consistent with **primary carnitine deficiency**. The condition is caused by a defect in the protein responsible for carnitine transport across the mitochondrial membrane. Without sufficient carnitine, fatty acids cannot be transported from the cytoplasm into the mitochondria as acyl-carnitine (carnitine shuttle). The mitochondria therefore cannot β-oxidize the fatty acids into acetyl CoA, the carbon substrate for the citric acid cycle. As a result, cardiac and skeletal myocytes cannot generate ATP from fatty acids (leading to muscle weakness, cardiomyopathy) and the liver is unable to synthesize **ketone bodies** (manifests as hypoketotic hypoglycemia).

Hypoketotic hypoglycemia is also seen in other fatty acid oxidation disorders (eg, acyl CoA dehydrogenase deficiency).

(Choice B) Arachidonic acid can be ingested or synthesized from phospholipids in the cell membrane. Its eicosanoid derivatives (eg, prostanoids, leukotrienes) are important modulators of inflammation. It is not affected by carnitine levels.

(Choice C) Glutathione is a tripeptide that can be synthesized from amino acids (glutamate, cysteine, and

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(Choice C) Glutathione is a tripeptide that can be synthesized from amino acids (glutamate, cysteine, and glycine). It is an important antioxidant and plays a role in DNA synthesis and repair.

(Choice D) Homocysteine is an amino acid that is synthesized from methionine. Using vitamin cofactors, it can be converted to cysteine (pyridoxine) or recycled into methionine (cobalamin).

(Choice E) Lactate is produced from pyruvate under anaerobic conditions. Patients with carnitine deficiency synthesize lactate normally but may produce increased lactate during times of catabolic stress due to inability to utilize fatty acids for energy production.

(Choice F) Palmitate is a fatty acid that can be ingested or synthesized from carbohydrates. Palmitate synthesis occurs in the cytosol and would not be affected by carnitine deficiency.

Educational objective:

Carnitine deficiency impairs fatty acid transport from the cytoplasm into mitochondria, preventing β-oxidation of fatty acids into acetyl CoA. This leads to cardiac and skeletal myocyte injury (lack of ATP from citric acid cycle) and impaired ketone body production by the liver during fasting periods.

References

- Primary carnitine deficiency: novel mutations and insights into the cardiac phenotype.

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A 6-month-old full-term boy is brought to the emergency department with lethargy and vomiting. He was born by uncomplicated spontaneous vaginal delivery and has been growing and developing normally. The patient was breastfed exclusively until 2 days ago when homemade pureed food was added to his diet. He has had no fever or diarrhea. His parents are healthy and he has had no sick contacts. Examination shows a pale, diaphoretic, and ill-appearing infant. Serum glucose is 30 mg/dL. Diagnostic testing confirms aldolase B deficiency. Which of the following should be removed from this patient's diet?

A. Amylose
B. Cellulose
C. Galactose
D. Glucose
E. Lactose
F. Maltose
G. Sucrose

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born by uncomplicated spontaneous vaginal delivery and has been growing and developing normally. The patient was breastfed exclusively until 2 days ago when homemade pureed food was added to his diet. He has had no fever or diarrhea. His parents are healthy and he has had no sick contacts. Examination shows a pale, diaphoretic, and ill-appearing infant. Serum glucose is 30 mg/dL. Diagnostic testing confirms aldolase B deficiency. Which of the following should be removed from this patient's diet?

- A. Amylose (1%)
- B. Cellulose (1%)
- C. Galactose (16%)
- D. Glucose (1%)
- E. Lactose (4%)
- F. Maltose (4%)
- ✓ G. Sucrose (71%)

Correct

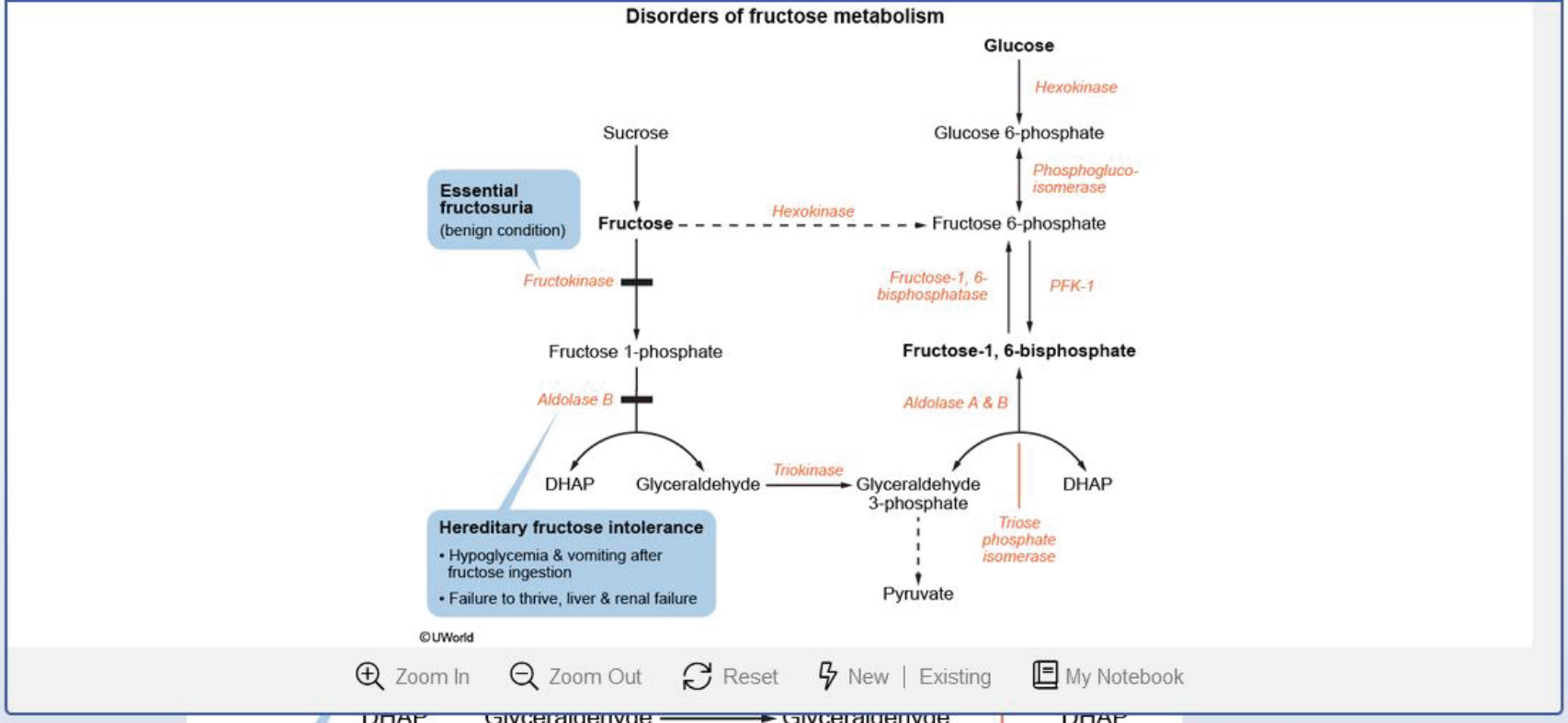
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Carbohydrates are classified as monosaccharides, disaccharides, and polysaccharides. Disaccharides and polysaccharides must be broken down to their monosaccharide components for energy production and utilization.

Aldolase B metabolizes fructose-1-phosphate, a product of fructose metabolism, to dihydroxyacetone phosphate (DHAP) and glyceraldehyde, which can then enter the glycolytic pathway. Aldolase B deficiency can result in **fructose-1-phosphate accumulation**; this toxic metabolite depletes intracellular phosphate and inhibits the activation of hepatic phosphorylase and gluconeogenesis. The resulting condition, hereditary fructose intolerance (eg, fructosemia), is an **autosomal recessive** disorder.

Because **gluconeogenesis is impaired**, fructosemia typically presents with life-threatening **hypoglycemia**. Consequences of hypoglycemia include lethargy, sweating, vomiting, and dehydration. These symptoms manifest after intake of fructose or sucrose, such as from formula or fruit. Strict abstinence from **dietary fructose and sucrose** can result in dramatic recovery.

(Choices A and D) Starch (similar to glycogen in mammals) is the major storage form of carbohydrates in plants and contains only glucose molecules. Starch consists of an unbranched portion composed of amylose and a branched portion called amylopectin. Patients with fructosemia have normal metabolism of

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amylose and a branched portion called amylopectin. Patients with fructosemia have normal metabolism of glucose.

(Choice B) Cellulose is a linear polysaccharide of glucose that is mainly present in the cell wall of plant cells. Cellulose is an insoluble, indigestible dietary fiber that is responsible for the bulk of fecal matter.

(Choices C, E, and F) Breast milk contains the disaccharides lactose (composed of galactose and glucose) and maltose (composed of 2 glucose molecules). Patients with aldolase B deficiency can consume these disaccharides as their breakdown will not produce fructose. However, patients with galactosemia cannot metabolize galactose in breast milk or cow's milk-based formula. These patients typically present in the first few days of life with jaundice, vomiting, poor feeding, and hepatomegaly.

Educational objective:

Aldolase B deficiency, or hereditary fructose intolerance, leads to accumulation of the toxic metabolite fructose-1-phosphate. Patients have hypoglycemia and vomiting when fructose or sucrose is consumed. Treatment involves strict removal of both carbohydrates from the diet.

References

- Inborn errors of carbohydrate metabolism.
- The biochemical basis of hereditary fructose intolerance.

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A research scientist develops an agent that specifically blocks the interaction of inositol triphosphate with its intracellular receptor. A study is then performed in which vascular smooth muscle cells are divided into 2 groups: an experimental group treated with the receptor blocker and an untreated control group. Both groups are exposed to phenylephrine. Compared to the control cells, decreased activity of which of the following enzymes is most likely to be observed in the experimental cells?

A. Adenylate cyclase
B. Lipoxygenase
C. Phosphodiesterase
D. Phospholipase C
E. Protein kinase C

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A. Adenylate cyclase (9%)
B. Lipoxygenase (0%)
C. Phosphodiesterase (4%)
D. Phospholipase C (36%)
✓ E. Protein kinase C (49%)

Correct

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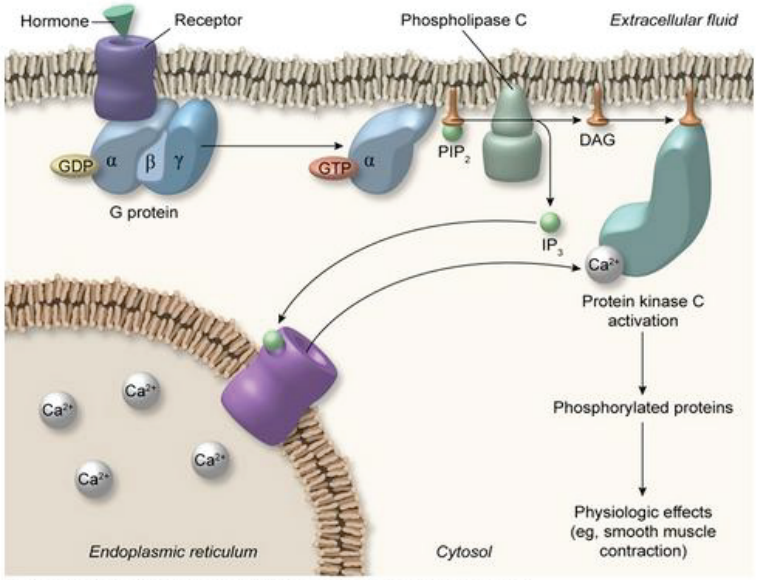
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Phosphatidylinositol 2nd messenger system



DAG = diacylglycerol; **GDP** = guanosine 5'-diphosphate; **GTP** = guanosine 5'-triphosphate; **IP_3** = inositol 1,4,5-trisphosphate; **PIP_2** = phosphatidylinositol 4,5-bisphosphate.

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IP_3 = inositol 1,4,5-trisphosphate; PIP_2 = phosphatidylinositol 4,5-bisphosphate.

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G protein-coupled receptors have a characteristic structure with 7 transmembrane regions, an extracellular domain, and an intracellular domain coupled with a G protein. In their inactivated state, G proteins exist as heterotrimers consisting of alpha, beta, and gamma subunits with GDP tightly bound to the alpha subunit. G proteins are activated after **ligand binding to the extracellular domain** of the receptor. The first step in activation occurs when GDP is exchanged for GTP on the alpha subunit. Once bound to GTP, the alpha subunit dissociates from the beta and gamma subunits and activates either adenylate cyclase or phospholipase C, depending on the ligand.

When phenylephrine binds to an alpha-1 receptor on vascular smooth muscle cells, the alpha subunit of the G protein (G_q) **activates phospholipase C**, which breaks down phosphatidylinositol bisphosphate into inositol triphosphate (IP_3) and diacylglycerol (DAG). DAG stimulates protein kinase C, which phosphorylates downstream intracellular proteins to produce its physiologic effects (eg, smooth muscle contraction). **IP_3** produces most of its effects by **increasing intracellular calcium**, which also **activates protein kinase C**. In the study described above, protein kinase C activity would be reduced in the experimental group compared to the control group as calcium release from the endoplasmic reticulum is interrupted.

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(Choice A) Activation of adenylate cyclase leads to the formation of cAMP and subsequent activation of protein kinase A. Protein kinase A phosphorylates intracellular proteins to produce its effects.

(Choice B) Lipoxygenase is an enzyme responsible for the formation of leukotrienes from arachidonic acid. It is not directly involved in the phosphatidylinositol second messenger system.

(Choice C) Phosphodiesterase is an enzyme that terminates the effects of ligands that act via cAMP or cGMP second messenger systems. It has no direct effect on the phosphatidylinositol second messenger system.

(Choice D) The activity of phospholipase C would be unchanged if IP_3 were blocked because phospholipase C exerts its effect before IP_3 in the phosphatidylinositol second messenger system.

Educational objective:

After a ligand binds to a G protein-coupled receptor that activates phospholipase C, membrane phospholipids are broken down into diacylglycerol (DAG) and inositol triphosphate (IP_3). Protein kinase C is subsequently activated by DAG and calcium; the latter is released from the endoplasmic reticulum under the influence of IP_3.

References

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A 14-year-old boy is brought to the emergency department after accidental ingestion of a chicken bone that lodged in his esophagus. Upper endoscopy is performed and the bone is successfully removed. However, the patient is incidentally found to have mild hypercalcemia on laboratory testing. On follow-up with his primary care provider 2 weeks later, he has no symptoms and clinical examination is unremarkable. Further questioning reveals that several of his family members also have mild hypercalcemia. Subsequent laboratory studies show a borderline high parathyroid hormone concentration, very low urinary calcium level, and normal 25-hydroxyvitamin D level. A mutation in which of the following receptors is most likely responsible for this patient's laboratory abnormalities?

A. Intracellular receptor with a DNA-binding domain
B. Membrane-bound receptor coupled with a G protein
C. Transmembrane ligand-gated ion channel
D. Transmembrane receptor associated with intrinsic tyrosine kinase activity
E. Transmembrane receptor causing activation of Janus kinase/STAT pathway

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lodged in his esophagus. Upper endoscopy is performed and the bone is successfully removed. However, the patient is incidentally found to have mild hypercalcemia on laboratory testing. On follow-up with his primary care provider 2 weeks later, he has no symptoms and clinical examination is unremarkable. Further questioning reveals that several of his family members also have mild hypercalcemia. Subsequent laboratory studies show a borderline high parathyroid hormone concentration, very low urinary calcium level, and normal 25-hydroxyvitamin D level. A mutation in which of the following receptors is most likely responsible for this patient's laboratory abnormalities?

A. ~~Intracellular receptor with a DNA-binding domain~~ (7%)

✓ B. Membrane-bound receptor coupled with a G protein (55%)

C. Transmembrane ligand-gated ion channel (20%)

D. ~~Transmembrane receptor associated with intrinsic tyrosine kinase activity~~ (9%)

E. ~~Transmembrane receptor causing activation of Janus kinase/STAT pathway~~ (7%)

Correct

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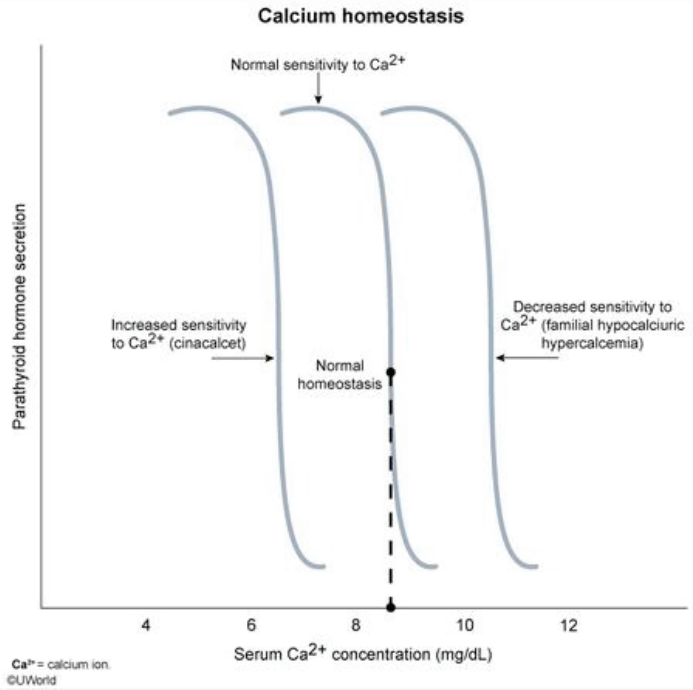
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Calcium-sensing receptors (CaSRs) are transmembrane **G_q protein–coupled** (metabotropic) receptors that regulate the secretion of parathyroid hormone (PTH) in response to changes in circulating calcium levels. Binding of calcium to CaSRs leads to the inhibition of PTH release, whereas low calcium levels allow increased PTH release.

Familial hypocalciuric hypercalcemia (FHH) is a benign autosomal dominant disorder caused by defective CaSRs in the parathyroid gland and kidneys. In FHH, higher serum calcium levels are required to suppress the secretion of PTH. This raises the set point of calcium-induced regulation of PTH secretion. Patients with FHH have mild asymptomatic hypercalcemia, reduced urinary excretion of calcium, and high normal or mildly elevated PTH.

(Choice A) Steroid hormones, thyroid hormone, and vitamin D act by binding to intracellular receptors with DNA-binding domains that interact with the regulatory DNA sequences of target genes.

(Choice C) Transmembrane ligand-gated ion channels (ionotropic receptors) allow a regulated flux of calcium, sodium, potassium, and chloride ions across the cell membrane. Neurotransmitters that work via ion channel–linked receptors include acetylcholine, serotonin, N-methyl-D-aspartate, and gamma-aminobutyric acid.

(Choice D) Insulin and insulin-like growth factor work by stimulating transmembrane receptors with

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ion channel–linked receptors include acetylcholine, serotonin, N-methyl-D-aspartate, and gamma-aminobutyric acid.

(Choice D) Insulin and insulin-like growth factor work by stimulating transmembrane receptors with intrinsic tyrosine kinase activity in the intracellular domain, initiating a downstream phosphorylation cascade.

(Choice E) Janus kinase (JAK) is a cytoplasmic protein activated by ligand binding to transmembrane receptors. JAKs activate cytoplasmic transcription factors called signal transducers and activators of transcription (STAT), which enter the nucleus to promote gene transcription. Examples of hormones using a JAK/STAT messenger system include erythropoietin, growth hormone, and prolactin.

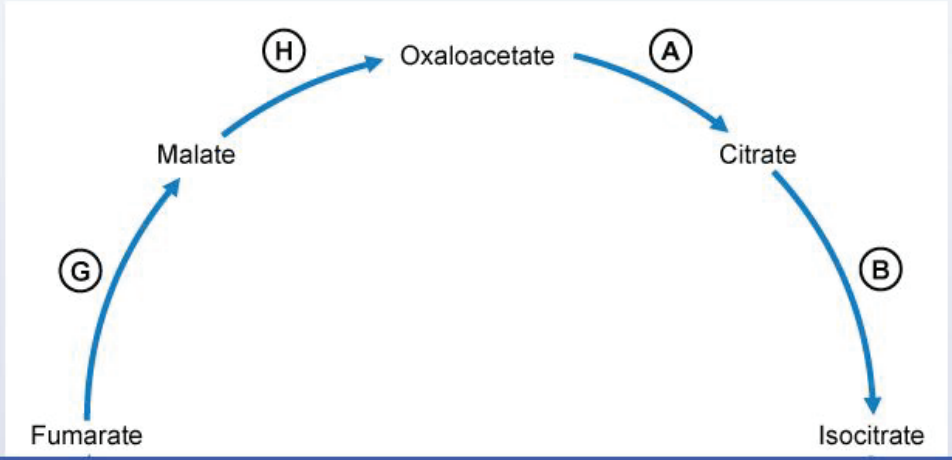
Educational objective:
Calcium-sensing receptors are G protein–coupled receptors that regulate the secretion of parathyroid hormone in response to changes in circulating calcium levels. Familial hypocalciuric hypercalcemia is a benign autosomal dominant disorder caused by defective calcium-sensing receptors in the parathyroid gland and kidneys.

References

- Familial hypocalciuric hypercalcaemia: a review.

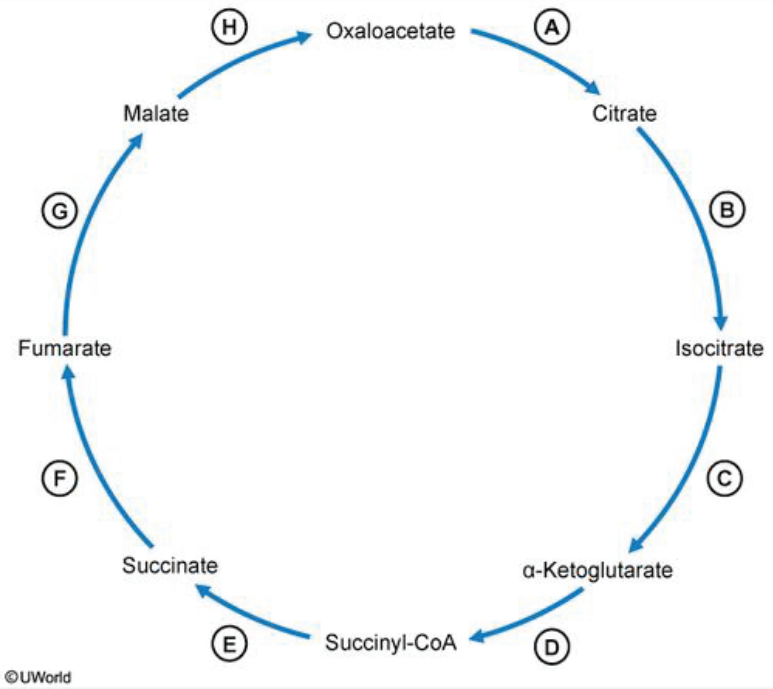
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A 43-year-old man prospecting for gold in Arizona becomes stuck in the desert after his truck breaks down. He brought a large supply of water with him but only a few granola bars as food. After 3 days, he is able to flag down a passing vehicle and obtain transportation to the nearest settlement. During this ordeal, his liver begins to synthesize large quantities of glucose from source molecules such as alanine, lactate, and glycerol. As part of this process, phosphoenolpyruvate is formed from oxaloacetate in a reaction that requires a specific nucleoside triphosphate as a cofactor. Which of the following reactions directly synthesizes this cofactor?



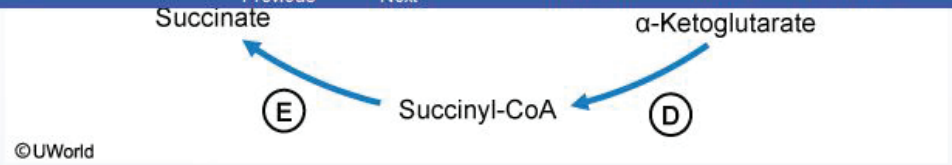
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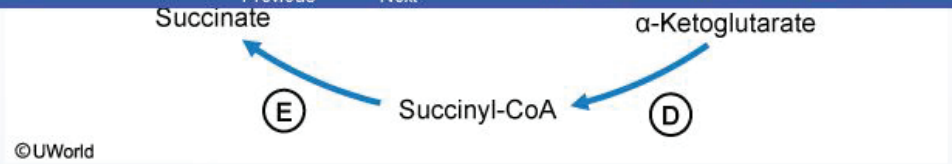
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- C.C
- D.D
- E.E
- F. F
- G.G
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- A. A (3%)
- B. B (3%)
- C. C (10%)
- D. D (20%)
- ✓ E. E (39%)
- F. F (11%)
- G. G (4%)
- H. H (5%)

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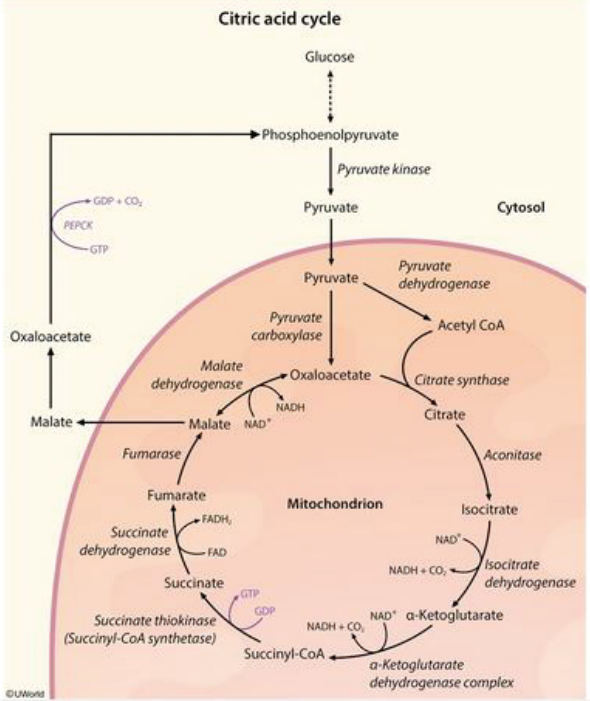
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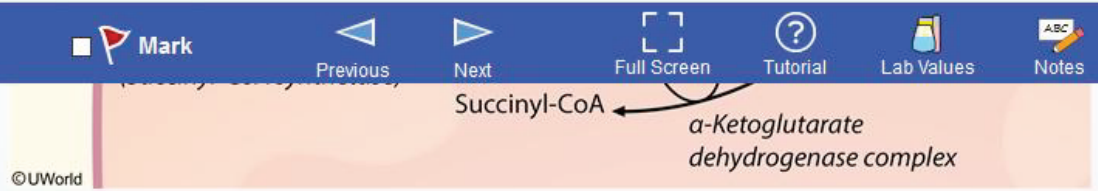
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The majority of ATP used for cellular processes is generated by the oxidation of acetate in the tricarboxylic acid (TCA) cycle. The enzymes of the TCA cycle are located in the mitochondria and generate reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) **(Choices C, D, F, and H)**. These molecules drive the process of oxidative phosphorylation, which converts their reducing potential into high-energy ATP via the electron transport chain.

ATP can also be generated by **substrate-level phosphorylation**, which involves the direct transfer of a phosphate group from a reactive intermediate to a nucleotide diphosphate (eg, ADP, GDP). **Succinyl-CoA synthetase** converts succinyl-CoA to succinate and uses the high-energy thioester present in succinyl-CoA to drive **GTP synthesis**. This GTP can then be used to transphosphorylate ADP to ATP, or it may be utilized by specific GTP-hydrolyzing enzymes, such as **phosphoenolpyruvate carboxykinase** (converts oxaloacetate to phosphoenolpyruvate during gluconeogenesis).

Educational objective:
GTP is synthesized by succinyl-CoA synthetase during the conversion of succinyl-CoA to succinate in the citric acid cycle. During gluconeogenesis, phosphoenolpyruvate carboxykinase uses GTP to synthesize

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nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) **(Choices C, D, F, and H)**. These molecules drive the process of oxidative phosphorylation, which converts their reducing potential into high-energy ATP via the electron transport chain.

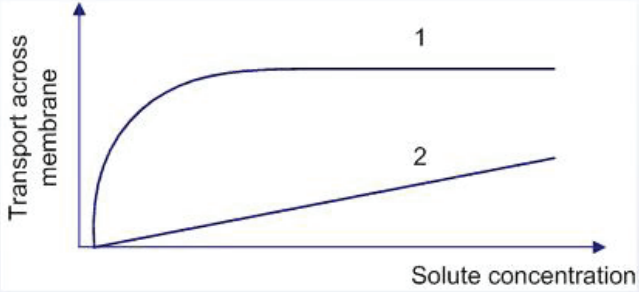
ATP can also be generated by **substrate-level phosphorylation**, which involves the direct transfer of a phosphate group from a reactive intermediate to a nucleotide diphosphate (eg, ADP, GDP). **Succinyl-CoA synthetase** converts succinyl-CoA to succinate and uses the high-energy thioester present in succinyl-CoA to drive **GTP synthesis**. This GTP can then be used to transphosphorylate ADP to ATP, or it may be utilized by specific GTP-hydrolyzing enzymes, such as **phosphoenolpyruvate carboxykinase** (converts oxaloacetate to phosphoenolpyruvate during gluconeogenesis).

Educational objective:
GTP is synthesized by succinyl-CoA synthetase during the conversion of succinyl-CoA to succinate in the citric acid cycle. During gluconeogenesis, phosphoenolpyruvate carboxykinase uses GTP to synthesize phosphoenolpyruvate from oxaloacetate.

Biochemistry	Biochemistry (General Principles)	Tca cycle
Subject	System	Topic

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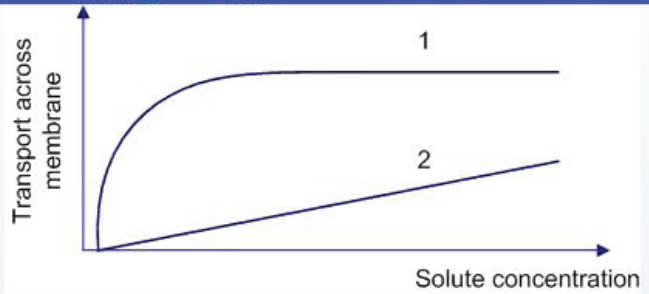
Two graphs illustrating the transport rate of solutes across the plasma membrane are shown on the slide below.



Which of the following best explains the difference in the shape of the curves?

A. Different amounts of membrane surface area for diffusion
B. Different degrees of membrane thickness
C. The 2 solutes have different molecular weights
D. The 2 solutes have different oil/water partition coefficients
E. The presence of a protein transporter

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Which of the following best explains the difference in the shape of the curves?

A. Different amounts of membrane surface area for diffusion (3%)

B. Different degrees of membrane thickness (1%)

C. The 2 solutes have different molecular weights (3%)

D. The 2 solutes have different oil/water partition coefficients (10%)

✓ E. The presence of a protein transporter (80%)

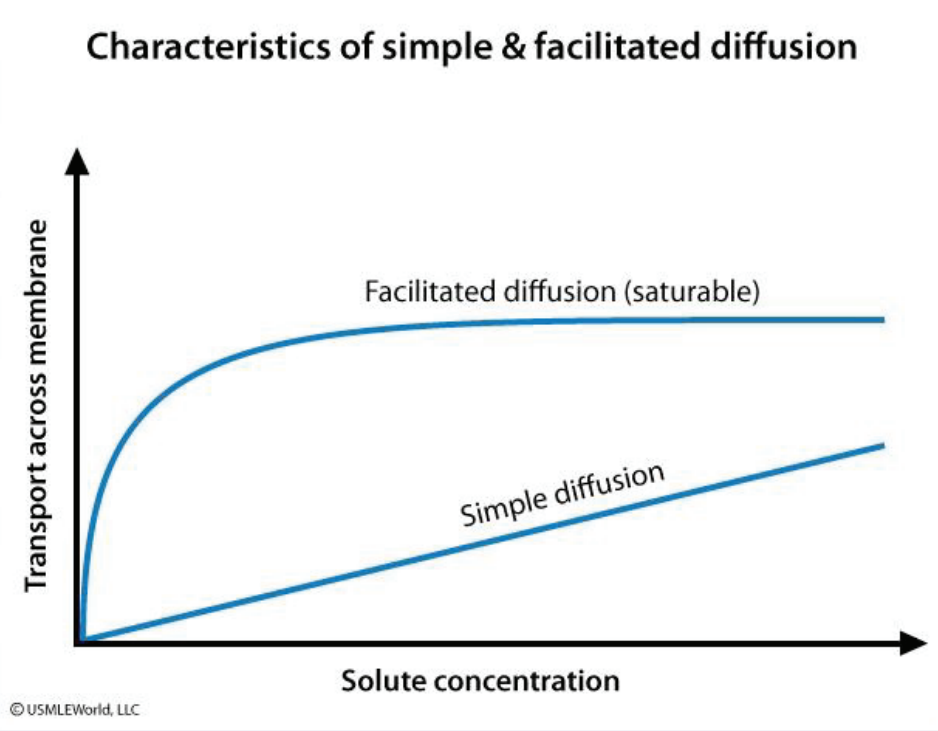
Correct

80%

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The image above illustrates the difference between the rate of transport of solute across the cell membrane in **simple diffusion** (line 2) and **carrier-mediated transport** (line 1).

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The image above illustrates the difference between the rate of transport of solute across the cell membrane in **simple diffusion** (line 2) and **carrier-mediated transport** (line 1).

There are two types of diffusion:

- Simple diffusion – molecules move through a membrane without the help of carrier proteins.
- Facilitated diffusion – requires carrier proteins.

Carrier proteins are typically transmembrane proteins that possess binding sites for the substrate they transport. Binding is followed by movement of the substrate across the cell membrane to the intracellular space, where it is released into the cytoplasm. Because there is a finite number of carrier proteins in the cell membrane, **transporter saturation** occurs with facilitated diffusion, and can be seen as a **flattening of the curve** (maximum diffusion speed), even as solute concentration continues to increase. This maximum rate of transport is referred to as the transport maximum (T_m) and is similar in principle to the V_{max} in standard enzyme kinetics.

(Choices A, B, C, D) These other factors are important for determining the rate of diffusion (ie, slope of the line), but would not explain the flattening of the curve in line 1 (which is best accounted for by saturation of a protein carrier). In general, the rate of diffusion increases with:

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(Choices A, B, C, D) These other factors are important for determining the rate of diffusion (ie, slope of the line), but would not explain the flattening of the curve in line 1 (which is best accounted for by saturation of a protein carrier). In general, the rate of diffusion increases with:

- Higher concentration gradients across the membrane
- Lower molecular weight
- Larger diffusion surface area
- Thinner membrane thickness

For molecules that move through the membrane via simple diffusion, the degree of lipophilicity is also important; molecules with a high oil-water partition coefficient are more easily able to cross the membrane and will diffuse faster.

Educational objective:
Carrier-mediated transport includes facilitated diffusion and active transport. Movement of substrate across the cell membrane by these mechanisms depends on the presence of carrier proteins that can become saturated at high substrate concentrations.

Biochemistry	Biochemistry (General Principles)	Cellular transports

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Succinate dehydrogenase (SDH) is an enzyme complex located within the inner mitochondrial membrane that catalyzes the oxidation of succinate to fumarate. An experiment is conducted to determine if malate alters the rate of SDH activity. Reaction velocity is measured with and without a fixed quantity of malate as succinate concentration is gradually increased. Obtained results are shown below.

Succinate concentration (mM)	Rate of reaction without malate (µmol/L/sec)	Rate of reaction with malate (µmol/L/sec)
2	80	40
8	200	120
16	280	200
64	400	400
128	400	400

Which of the following is the most accurate statement about malate in this experiment?

A. It alters the maximal velocity of the reaction

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8	200	120
16	280	200
64	400	400
128	400	400

Which of the following is the most accurate statement about malate in this experiment?

A. It alters the maximal velocity of the reaction
B. It binds the enzyme at a different site than succinate
C. It covalently binds the enzyme
D. It decreases affinity of the enzyme for succinate
E. It is a competitive inhibitor of the enzyme

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8	200	120
16	280	200
64	400	400
128	400	400

Which of the following is the most accurate statement about malate in this experiment?

A. It alters the maximal velocity of the reaction (3%)
B. It binds the enzyme at a different site than succinate (8%)
C. It covalently binds the enzyme (1%)
D. It decreases affinity of the enzyme for succinate (10%)
E. It is a competitive inhibitor of the enzyme (76%)

Correct

76%
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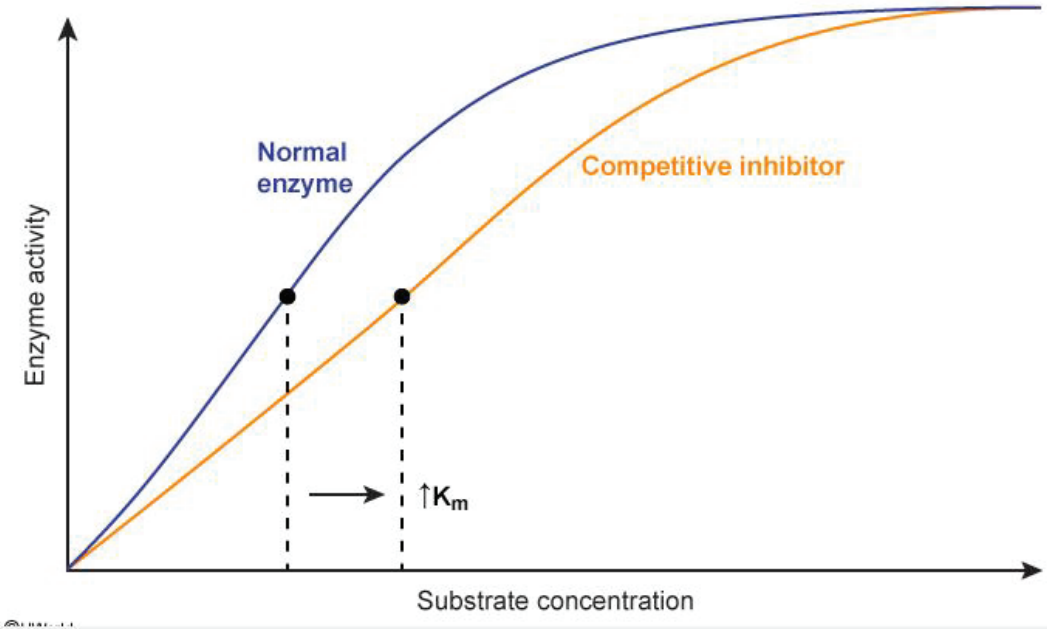
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Competitive inhibition



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Substrate concentration

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The Michaelis-Menten model describes the behavior of enzyme-driven reactions by comparing the rate of reaction (V) to the concentration of the substrate (S). Maximal velocity (V_{max}) represents the speed at which the reaction occurs when the enzyme's active sites are completely saturated with substrate. The Michaelis constant (K_m) defines the substrate concentration at which half of the enzyme's binding sites are occupied by substrate (½ V_{max}). Substrates with high affinity for the enzyme typically have a low K_m.

Competitive inhibition occurs when an inhibitor binds to an enzyme and prevents it from binding the substrate. Most competitive inhibitors (including malate) **bind at the active site** (substrate-binding pocket) and physically impede substrate binding. Because these inhibitors compete with the substrate for binding to the active site, additional substrate is required to reach ½ V_{max}, thereby **increasing apparent K_m**. Competitive inhibitors have no effect on enzyme function, and therefore **V_{max} is unchanged**.

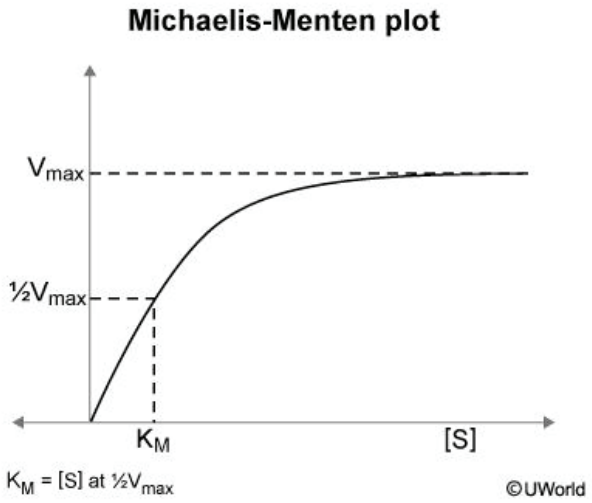
In this example, V_{max} remains constant (at 400 µmol/L/sec) while K_m increases (from 8 to 16 mM) in the presence of malate. Therefore, malate is a competitive inhibitor of succinate dehydrogenase for succinate.

(Choice A) V_{max} depends on how fast an enzyme can catalyze a reaction when there are enough substrate molecules to fully saturate its active sites. Competitive inhibitors do not affect V_{max}, as higher substrate

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Substrate concentration

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(Choice A) V_{max} depends on how fast an enzyme can catalyze a reaction when there are enough substrate molecules to fully saturate its active sites. Competitive inhibitors do not affect V_{max}, as higher substrate concentrations are able to overcome the inhibition.

(Choice B) Most competitive inhibitors, such as malate, bind in the substrate-binding pocket. In contrast, most noncompetitive inhibitors bind at allosteric sites, resulting in a conformational change of the enzyme that decreases enzymatic activity and slows the rate of reaction (V_{max}). Noncompetitive inhibition does not change the apparent K_m and cannot be overcome with higher substrate concentrations.

(Choice C) Irreversible inhibitors bind to enzymes through strong covalent bonds; this typically renders the enzyme permanently ineffective, decreasing the V_{max}.

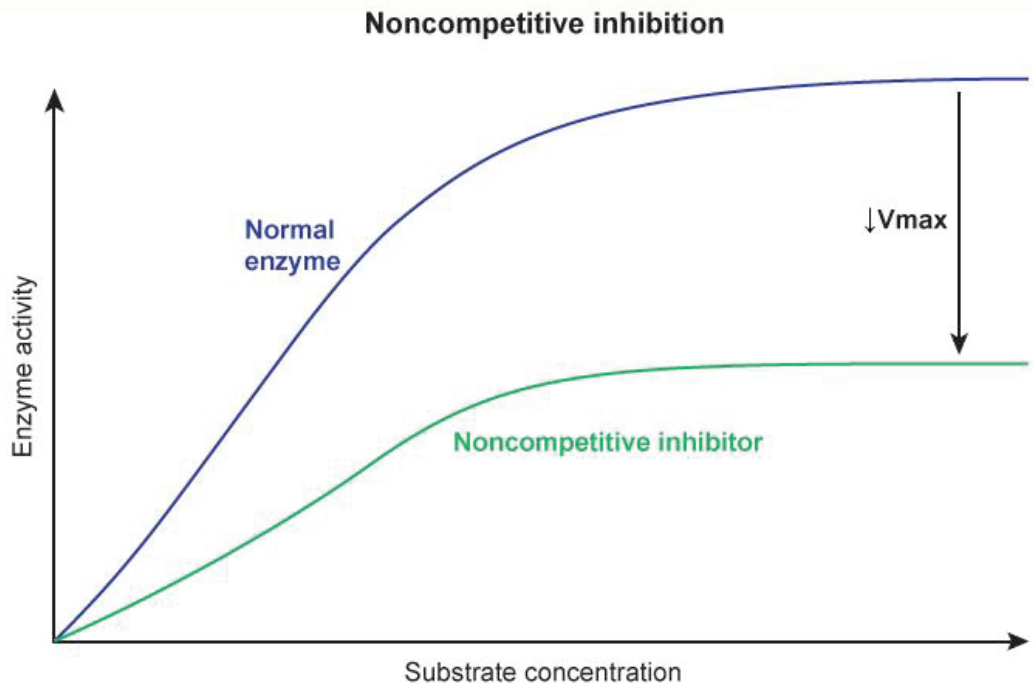
(Choice D) Competitive inhibitors interfere with substrate binding due to the inhibitor's own high affinity for the enzyme's active site. This causes the measured K_m value to increase; however, the actual enzyme affinity for the substrate remains unchanged.

Educational objective:
Competitive inhibitors compete with substrate for active binding sites on enzymes. Additional substrate is required to achieve the same rate of reaction, increasing the measured value of the Michaelis constant

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(Choice B) Most competitive inhibitors, such as malate, bind in the substrate-binding pocket. In contrast, most noncompetitive inhibitors bind at allosteric sites, resulting in a conformational change of the enzyme that decreases enzymatic activity and slows the rate of reaction (V_{max}). Noncompetitive inhibition does not change the apparent K_m and cannot be overcome with higher substrate concentrations.

(Choice C) Irreversible inhibitors bind to enzymes through strong covalent bonds; this typically renders the enzyme permanently ineffective, decreasing the V_{max}.

(Choice D) Competitive inhibitors interfere with substrate binding due to the inhibitor's own high affinity for the enzyme's active site. This causes the measured K_m value to increase; however, the actual enzyme affinity for the substrate remains unchanged.

Educational objective:
Competitive inhibitors compete with substrate for active binding sites on enzymes. Additional substrate is required to achieve the same rate of reaction, increasing the measured value of the Michaelis constant (K_m). Competitive inhibitors do not affect enzyme function; therefore, maximal velocity (V_{max}) is unchanged in their presence.

Biochemistry	Biochemistry (General Principles)	Enzyme kinetics

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A 5-month-old boy is brought to the office due to poor feeding. His mother says that he has difficulty holding his head up while breastfeeding and his suckling seems weaker than it used to be. His current weight is between the 5th-10th percentile, and length and head circumference are tracking along the 25th percentile. Physical examination shows hepatomegaly and hypotonia in all 4 limbs. Cardiac auscultation reveals a gallop rhythm, and chest x-ray shows severe cardiomegaly. Muscle biopsy shows enlarged lysosomes containing periodic acid-Schiff (PAS)-positive material. Which of the following enzymes is most likely deficient in this patient?

A. Acid α-glucosidase
B. Debrancher enzyme
C. Galactokinase
D. Glucose-6-phosphatase
E. Glycogen phosphorylase
F. Pyruvate kinase

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holding his head up while breastfeeding and his suckling seems weaker than it used to be. His current weight is between the 5th-10th percentile, and length and head circumference are tracking along the 25th percentile. Physical examination shows hepatomegaly and hypotonia in all 4 limbs. Cardiac auscultation reveals a gallop rhythm, and chest x-ray shows severe cardiomegaly. Muscle biopsy shows enlarged lysosomes containing periodic acid-Schiff (PAS)-positive material. Which of the following enzymes is most likely deficient in this patient?

- A. Acid α-glucosidase (56%)
- B. Debrancher enzyme (14%)
- C. Galactokinase (4%)
- D. Glucose-6-phosphatase (8%)
- E. Glycogen phosphorylase (12%)
- F. Pyruvate kinase (2%)

Correct

56%

42 secs

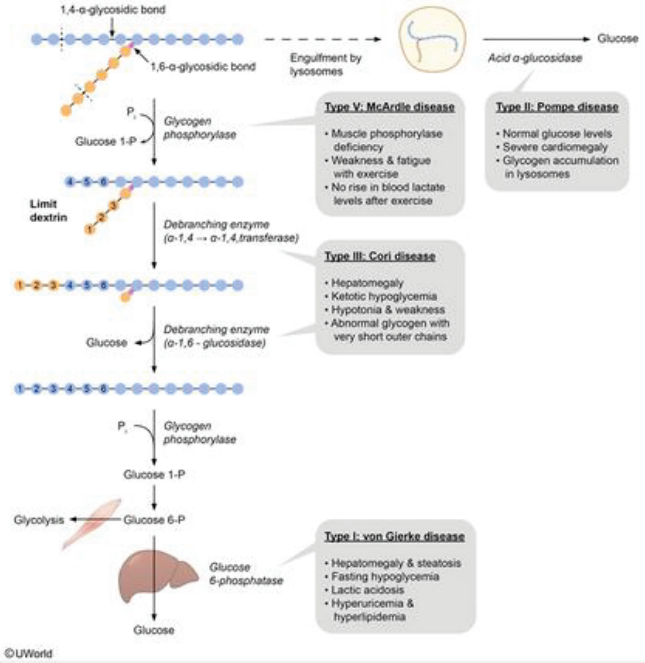
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Impairments in glycogenolysis



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This patient most likely has glycogen storage disease type II (**Pompe disease**). This condition is caused by deficiency of **acid α-glucosidase** (acid maltase), an enzyme responsible for breaking down glycogen within the acidic environment of lysosomes. Although most glycogen is degraded in the cytoplasm, a small amount is inadvertently engulfed by lysosomes, especially in cells containing high amounts of glycogen such as hepatocytes and myocytes. As such, deficiency of acid maltase results in pathologic accumulation of glycogen within liver and muscle lysosomes. Cardiac and skeletal muscle are particularly susceptible, as the ballooning lysosomes interfere with contractile function.

The classic form of the disease presents in early infancy with marked **cardiomegaly**, severe generalized **hypotonia**, macroglossia, and hepatomegaly. Blood glucose levels are normal, unlike with glycogen storage diseases that primarily affect the liver (eg, von Gierke). A key distinguishing feature is that muscle biopsy will show accumulation of **glycogen in lysosomes**.

(Choices B, D, and E) Other glycogen storage diseases are caused by deficiencies of glucose-6-phosphatase, glycogen phosphorylase, and debrancher enzyme. However, glycogen accumulation within lysosomal vacuoles is specific for acid α-glucosidase deficiency.

(Choice C) Galactokinase catalyzes the phosphorylation of galactose to galactose-1-phosphate in the first committed step of galactose catabolism. Galactokinase deficiency causes neonatal cataract formation due to accumulation of galactitol in the lens.

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6-phosphatase, glycogen phosphorylase, and debrancher enzyme. However, glycogen accumulation within lysosomal vacuoles is specific for acid α-glucosidase deficiency.

(Choice C) Galactokinase catalyzes the phosphorylation of galactose to galactose-1-phosphate in the first committed step of galactose catabolism. Galactokinase deficiency causes neonatal cataract formation due to accumulation of galactitol in the lens.

(Choice F) Pyruvate kinase deficiency causes chronic hemolytic anemia, splenomegaly, and iron overload as a result of impaired erythrocyte survival.

Educational objective:
Acid maltase (α-glucosidase) deficiency presents in early infancy with cardiomegaly, macroglossia, and profound muscular hypotonia. Abnormal glycogen accumulation within lysosomal vesicles is seen on muscle biopsy.

References

- Lysosomal dysfunction in muscle with special reference to glycogen storage disease type II.

Biochemistry	Biochemistry (General Principles)	Glycogen storage disease
Subject	System	Topic

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An 8-year-old boy is evaluated for exercise intolerance. The patient experiences fatigue, muscle pain, and cramps during exercise as well as severe muscle stiffness following strenuous activity. Physical examination is unremarkable. A forearm ischemic exercise test is performed by applying a blood pressure cuff on the patient's exercising forearm and sampling blood lactate several minutes after the exercise. The patient's blood samples show no rise in lactate levels. Biochemical analysis of a muscle biopsy reveals absent lactate dehydrogenase activity. In this patient, strenuous exercise leads to inhibition of glycolysis in skeletal muscle due to intracellular depletion of which of the following substances?

A. AMP
B. Carnitine
C. Citrate
D. $FADH_2$
E. NAD^+
F. Pyruvate

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cramps during exercise as well as severe muscle stiffness following strenuous activity. Physical examination is unremarkable. A forearm ischemic exercise test is performed by applying a blood pressure cuff on the patient's exercising forearm and sampling blood lactate several minutes after the exercise. The patient's blood samples show no rise in lactate levels. Biochemical analysis of a muscle biopsy reveals absent lactate dehydrogenase activity. In this patient, strenuous exercise leads to inhibition of glycolysis in skeletal muscle due to intracellular depletion of which of the following substances?

A. AMP (6%)
B. Carnitine (3%)
C. Citrate (3%)
D. $FADH_2$ (2%)
E. NAD^+ (64%)
F. Pyruvate (18%)

Correct

64%
Answered correctly

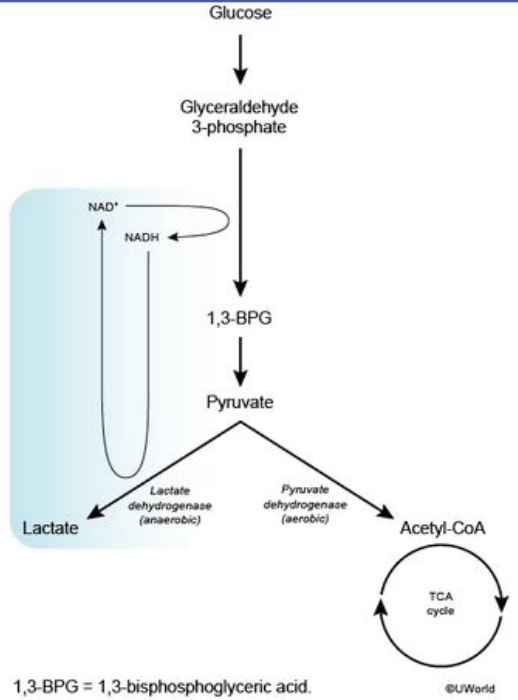
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1,3-BPG = 1,3-bisphosphoglyceric acid.

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In glycolysis, glucose is metabolized to pyruvate. Under aerobic conditions, pyruvate is converted to acetyl-CoA to enter the tricarboxylic acid (TCA) cycle. When oxygen is depleted (eg, in exercising muscle), pyruvate is converted to lactate (**anaerobic glycolysis**).

During glycolysis, glyceraldehyde-3-phosphate (G3P) is converted to 1-3-bisphosphoglycerate (BPG) by the enzyme G3P dehydrogenase. This enzyme reduces NAD^+ to NADH. NAD^+ is present in limited amounts in most cells, and it must be regenerated from NADH for glycolysis to continue. Under aerobic conditions, NAD^+ is converted to NADH in the TCA cycle. NADH is then reconverted to NAD^+ in the electron transport chain as the energy in NADH is utilized to synthesize ATP.

In anaerobic glycolysis, **NAD+** is **regenerated** from NADH when pyruvate is converted to lactate via **lactate dehydrogenase**. In patients with lactate dehydrogenase deficiency, glycolysis is inhibited in strenuously exercising muscle as muscle cells cannot regenerate NAD^+. Consequently, high-intensity physical activity leads to muscle breakdown, pain, and fatigue as insufficient amounts of energy are being produced in the exercising muscle.

(Choice A) During muscle contraction, glycogen is broken down via glycogen phosphorylase for energy production by the glycolytic pathway. Epinephrine causes cyclic AMP-mediated phosphorylation of

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produced in the exercising muscle.

(Choice A) During muscle contraction, glycogen is broken down via glycogen phosphorylase for energy production by the glycolytic pathway. Epinephrine causes cyclic AMP-mediated phosphorylation of glycogen phosphorylase, which activates this enzyme. Non-phosphorylation-dependent activation of glycogen phosphorylase can occur during muscle contraction via increased intracellular calcium concentrations and via AMP under extreme conditions.

(Choice B) Carnitine is an amino acid derivative responsible for transporting fatty acids into the mitochondria for beta-oxidation. Carnitine is synthesized from lysine and methionine; vitamin C is essential for this synthesis.

(Choice C) Citrate is formed from the condensation of acetyl CoA with oxaloacetate in the first step of the TCA cycle. Increased citrate concentrations decrease glycolysis as citrate is a powerful allosteric inhibitor of phosphofructokinase-1. In exercising muscles under anaerobic conditions, oxidative phosphorylation of glucose through the citric acid cycle is not a dominant pathway; therefore, excess citrate is not produced.

(Choice D) $FADH_2$ is not produced in glycolysis. $FADH_2$ is produced from FAD during the conversion of succinate to fumarate in the TCA cycle by the enzyme succinate dehydrogenase.

(Choice F) In glycolysis, pyruvate is formed from phosphoenolpyruvate by a unidirectional enzyme called

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for this synthesis.

(Choice C) Citrate is formed from the condensation of acetyl CoA with oxaloacetate in the first step of the TCA cycle. Increased citrate concentrations decrease glycolysis as citrate is a powerful allosteric inhibitor of phosphofructokinase-1. In exercising muscles under anaerobic conditions, oxidative phosphorylation of glucose through the citric acid cycle is not a dominant pathway; therefore, excess citrate is not produced.

(Choice D) $FADH_2$ is not produced in glycolysis. $FADH_2$ is produced from FAD during the conversion of succinate to fumarate in the TCA cycle by the enzyme succinate dehydrogenase.

(Choice F) In glycolysis, pyruvate is formed from phosphoenolpyruvate by a unidirectional enzyme called pyruvate kinase. In the absence of lactate dehydrogenase activity, pyruvate will accumulate in the cell under anaerobic conditions.

Educational objective:

Under anaerobic conditions, NADH transfers electrons to pyruvate to form lactate and regenerate NAD^+. NAD^+ is required to convert glyceraldehyde-3-phosphate to 1-3-bisphosphoglycerate in glycolysis.

References

- Lactate dehydrogenase M-subunit deficiencies: clinical features, metabolic background, and genetic heterogeneities

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Foreign antigen recognition at the cell surface by cytotoxic T-lymphocytes stimulates a response that results in rapid cell death. Which of the following act as effectors of this response?

A. Matrix metalloproteinases
B. Acid hydrolases
C. Caspases
D. Phospholipase A_2
E. Protein kinase A

Submit

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Foreign antigen recognition at the cell surface by cytotoxic T-lymphocytes stimulates a response that results in rapid cell death. Which of the following act as effectors of this response?

- A. Matrix metalloproteinases (6%)
- B. Acid hydrolases (9%)
- ✓ C. Caspases (78%)
- D. Phospholipase A_2 (3%)
- E. Protein kinase A (2%)

Correct

78%
Answered correctly

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Explanation

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The two primary modes of cell death are necrosis (which is induced by injury) and apoptosis (which is initiated by the host organism in response to cell damage, age-related atrophy, or specific stages of embryogenesis). Apoptosis is helpful in the elimination of cells that are no longer necessary and in the maintenance of a constant number of cells in rapidly growing tissues. Tumor cells, for example, die by apoptosis. The death of B and T lymphocytes and virally-infected cells also occurs through apoptosis. The remains of cells that die by this method are phagocytized by macrophages.

The process of apoptosis involves the following steps:

1. Initiation: Apoptosis is triggered by different stimuli and can occur through either the intrinsic, mitochondria-mediated pathway or the extrinsic, receptor-initiated pathway. Cells damaged by ultraviolet light, heat, hypoxia, toxins, or radiation display intrinsic apoptotic signals (eg, phosphatidylserine or thrombospondin) on their plasma membranes. Extrinsic apoptosis, in contrast, is induced by the tumor necrosis factor (TNF) when bound to tumor necrosis factor receptor 1 (TNFR1) or the Fas ligand when bound to cell surface receptor Fas.
2. Control: Intrinsic apoptosis is mediated by a group of bcl-2 proteins. Some of the components of this system are pro-apoptotic (eg, Bak, Bax, and Bim proteins), while others are anti-apoptotic (eg, Bcl-x and Bcl-2 proteins). Apoptotic signals tip the balance between these two forces, resulting in changes

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2. Control: Intrinsic apoptosis is mediated by a group of bcl-2 proteins. Some of the components of this system are pro-apoptotic (eg, Bak, Bax, and Bim proteins), while others are anti-apoptotic (eg, Bcl-x and Bcl-2 proteins). Apoptotic signals tip the balance between these two forces, resulting in changes of the inner mitochondrial membrane. These changes are responsible for the formation of the mitochondrial permeability transition (MPT) and the release of cytochrome c and other pro-apoptotic proteins into the cytoplasm, which then activate caspases. In extrinsic apoptosis, the binding of the death ligand and the death receptor allows for pro-caspase molecules to be brought into close proximity.
3. Destruction: Both the intrinsic and extrinsic pathways converge at this step, resulting in caspase activation. Caspases are proteolytic enzymes that destroy cell components. They contain cysteine and are able to cleave aspartic acid residues (**c**ysteine-**asp**artic-acid-prote**ases**). The eleven caspases that have been identified are classified as either initiator or effector caspases. Initiator caspases activate the effector caspases, which then cleave the cellular proteins.

(Choice A) Metalloproteinases are zinc-containing enzymes that degrade the components of the extracellular matrix (eg, collagen, laminin, fibronectin). Metalloproteinases are essential for proper tissue remodeling during wound healing.

(Choice B) Acid hydrolases do not participate in apoptosis.

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caspases activate the effector caspases, which then cleave the cellular proteins.

(Choice A) Metalloproteinases are zinc-containing enzymes that degrade the components of the extracellular matrix (eg, collagen, laminin, fibronectin). Metalloproteinases are essential for proper tissue remodeling during wound healing.

(Choice B) Acid hydrolases do not participate in apoptosis.

(Choice D) Phospholipase A_2 does not participate in apoptosis.

(Choice E) Protein kinase A is a component of the cAMP-associated signaling system. The binding of a ligand to a G-protein-linked receptor results in adenylyl cyclase activation and the release of cAMP. Elevated levels of cAMP activate protein kinase A.

Educational Objective:
Apoptosis can occur through either the intrinsic (mitochondria-mediated) pathway or the extrinsic (receptor-initiated) pathway. Both pathways converge in the activation of caspases. Caspases are proteolytic enzymes that cleave cellular proteins.

Biochemistry	Biochemistry (General Principles)	Cell mediated immunity
Subject	System	Topic

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As part of an experiment, healthy volunteers undergo a 12-hour fast and then drink a solution containing radiolabeled alanine. Consecutive blood samples are drawn every 15 minutes for the next 3 hours. Initial blood samples detect the radiolabeled alanine, but analysis of later samples shows that the radiotracer is present in blood primarily in the form of glucose. Before alanine can be converted to glucose, its amino group is transferred to which of the following?

A. α-Ketoglutarate
B. L-citrulline
C. Malate
D. Citrate
E. Oxaloacetate

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As part of an experiment, healthy volunteers undergo a 12-hour fast and then drink a solution containing radiolabeled alanine. Consecutive blood samples are drawn every 15 minutes for the next 3 hours. Initial blood samples detect the radiolabeled alanine, but analysis of later samples shows that the radiotracer is present in blood primarily in the form of glucose. Before alanine can be converted to glucose, its amino group is transferred to which of the following?

- ✓ A. α-Ketoglutarate (61%)
- B. L-citrulline (5%)
- C. Malate (7%)
- D. Citrate (5%)
- E. Oxaloacetate (19%)

Correct

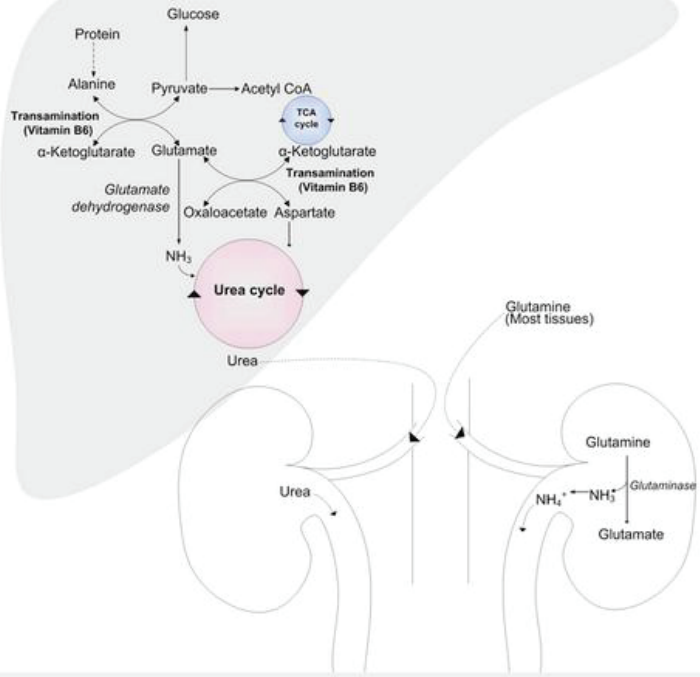
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Alanine and glutamine play an important role in transporting nitrogen throughout the body. Glutamine is produced by most body tissues and is catabolized primarily by the gut and kidney for maintenance of cellular metabolism and acid-base regulation, respectively. A significant portion of the glutamine used by these tissues is converted to alanine and released into the circulation. Alanine is also released by skeletal muscle tissue during protein catabolism as part of the glucose-alanine cycle that helps remove excess nitrogen. Alanine is then transported to the liver, where it serves as a vehicle for nitrogen disposal and as a source of carbon skeletons for gluconeogenesis.

In the liver, alanine is transaminated by alanine aminotransferase to pyruvate with the amino group being transferred to α-ketoglutarate to form glutamate. Almost all aminotransferase enzymes use α-ketoglutarate as the amino group acceptor. Thus, amino groups are funneled into glutamate during protein catabolism. Glutamate is further metabolized by the enzyme glutamate dehydrogenase, which liberates free ammonia and regenerates α-ketoglutarate. Ammonia then enters the urea cycle to form urea, the primary disposal form of nitrogen in humans. Urea subsequently enters the blood and is excreted in the urine.

(Choices C, D, and E) Malate, citrate, and oxaloacetate are all intermediates of the tricarboxylic acid cycle.

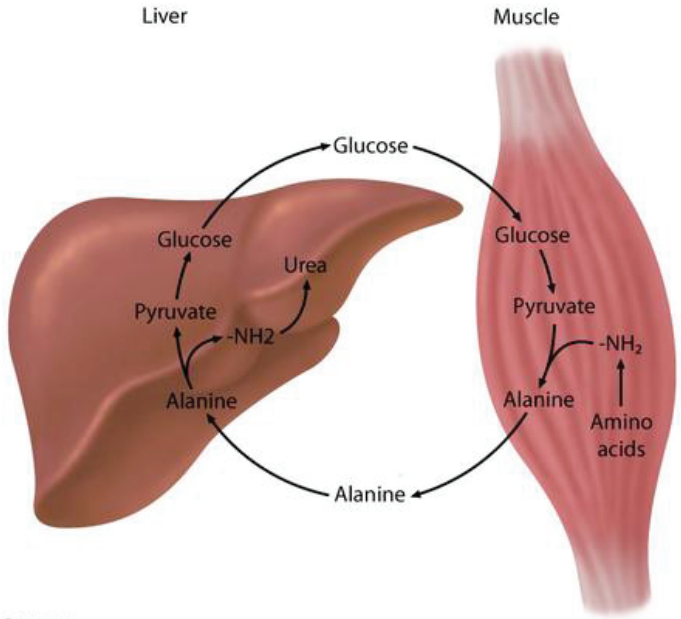
(Choice B) L-citrulline is an amino acid produced as an intermediate in the conversion of ornithine to argininosuccinate during the hepatic urea cycle.

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Alanine and glutamine play an important role in transporting nitrogen throughout the body. Glutamine is

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Glucose-alanine cycle



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arginiosuccinate during the hepatic urea cycle

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Glutamate is further metabolized by the enzyme glutamate dehydrogenase, which liberates free ammonia and regenerates α-ketoglutarate. Ammonia then enters the urea cycle to form urea, the primary disposal form of nitrogen in humans. Urea subsequently enters the blood and is excreted in the urine.

(Choices C, D, and E) Malate, citrate, and oxaloacetate are all intermediates of the tricarboxylic acid cycle.

(Choice B) L-citrulline is an amino acid produced as an intermediate in the conversion of ornithine to argininosuccinate during the hepatic urea cycle.

Educational objective:
Alanine is the major amino acid responsible for transferring nitrogen to the liver for disposal. During the catabolism of proteins, amino groups are transferred to α-ketoglutarate to form glutamate. Glutamate is then processed in the liver to form urea, the primary disposal form of nitrogen in humans. Free ammonia is also excreted into the urine by the kidney for regulation of acid-base status.

Biochemistry	Biochemistry (General Principles)	Tca cycle
Subject	System	Topic

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A 23-year-old apparently healthy man who recently immigrated to the United States comes to an outpatient clinic to establish care. When asked about his past medical history, he says that he has no significant medical problems. However, his mother told him that he was born with "a problem metabolizing sugar." The patient maintains no dietary restrictions and regularly eats vegetables, fruits, meats, and processed foods. Urine samples show a repeatedly positive copper reduction test, but glucose oxidase dipstick testing is negative. Which of the following enzymes is most likely to be deficient in this patient?

A. Acid α-glucosidase
B. Aldolase B
C. Fructokinase
D. Galactose-1-phosphate uridyl transferase
E. Lactase

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A 23-year-old apparently healthy man who recently immigrated to the United States comes to an outpatient clinic to establish care. When asked about his past medical history, he says that he has no significant medical problems. However, his mother told him that he was born with "a problem metabolizing sugar." The patient maintains no dietary restrictions and regularly eats vegetables, fruits, meats, and processed foods. Urine samples show a repeatedly positive copper reduction test, but glucose oxidase dipstick testing is negative. Which of the following enzymes is most likely to be deficient in this patient?

A. Acid α-glucosidase (8%)
B. Aldolase B (12%)
C. Fructokinase (62%)
D. Galactose-1-phosphate uridyl transferase (10%)
E. Lactase (6%)

Correct

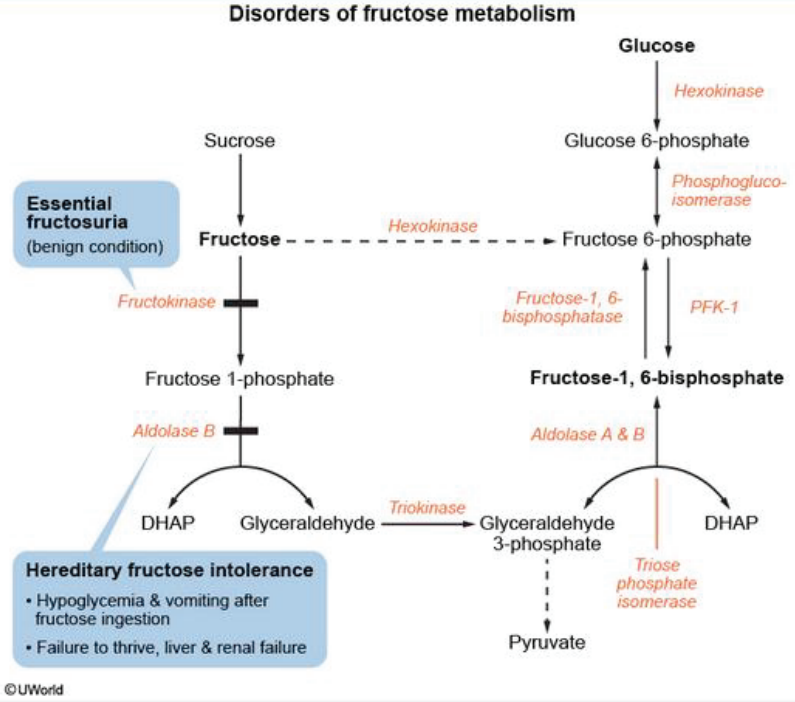
62% Answered correctly

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This asymptomatic patient with history of an inborn error of sugar metabolism most likely has **essential fructosuria**. This benign, autosomal recessive disorder causes some of the dietary fructose load to be secreted in the urine unchanged due to defective metabolism by **fructokinase**. Fructose, similar to glucose and galactose, is a **reducing sugar** and can be detected by a **copper reduction test**, which nonspecifically detects the presence of reducing sugar. A urine dipstick, however, uses glucose oxidase to ascertain the presence of urinary glucose and will not test positive in the presence of fructose or galactose.

(Choice A) Acid α-glucosidase (or acid maltase) deficiency causes glycogen storage disease type II (Pompe disease). Affected infants have cardiomyopathy, muscle weakness, and hypotonia.

(Choice B) Aldolase B deficiency is a life-threatening disorder caused by the inability to metabolize fructose-1-phosphate (a toxic intermediate that accumulates in cells and depletes intracellular phosphate). Patients become acutely symptomatic after ingesting fructose-containing foods and eventually develop liver failure. Treatment includes elimination of dietary fructose.

(Choice D) Galactosemia is an autosomal recessive disorder caused by galactose-1-phosphate uridyl transferase deficiency. It is characterized by neonatal jaundice, vomiting, cataract formation, hepatomegaly, and failure to thrive. Treatment includes elimination of all milk products from the diet and

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(Choice D) Galactosemia is an autosomal recessive disorder caused by galactose-1-phosphate uridyl transferase deficiency. It is characterized by neonatal jaundice, vomiting, cataract formation, hepatomegaly, and failure to thrive. Treatment includes elimination of all milk products from the diet and feeding with soy-based infant formula.

(Choice E) Lactase is a mucosal enzyme responsible for the digestion of lactose. Acquired lactase deficiency is the most common cause of selective carbohydrate malabsorption. Patients with lactase deficiency experience gastrointestinal symptoms (eg, bloating, diarrhea) following the ingestion of dairy products.

Educational objective:
Unlike hereditary fructose intolerance (aldolase B deficiency) and classic galactosemia (galactose-1-phosphate uridyl transferase deficiency), essential fructosuria (fructokinase deficiency) is a benign disorder. Although affected patients are asymptomatic, their urine will test positive for a reducing sugar due to the presence of unmetabolized fructose.

Biochemistry	Biochemistry (General Principles)	Fructose metabolism
Subject	System	Topic

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A 7-day-old neonate born to a 28-year-old woman is brought to the office due to progressive lethargy, vomiting, and poor feeding. The mother reports an uneventful pregnancy and perinatal course. She exclusively breastfeeds the infant and has no medical problems in any of her other children. On examination, the infant is somnolent and dehydrated with decreased muscle tone. Laboratory studies reveal metabolic acidosis with an elevated anion gap, ketosis, and hypoglycemia. Further evaluation reveals a markedly elevated propionic acid level due to defective conversion of propionyl-CoA to methylmalonyl-CoA. This patient is most likely unable to use which of the following amino acids for energy production?

- A. Alanine
- B. Aspartate
- C. Glutamate
- D. Lysine
- E. Phenylalanine
- F. Valine

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exclusively breastfeeds the infant and has no medical problems in any of her other children. On examination, the infant is somnolent and dehydrated with decreased muscle tone. Laboratory studies reveal metabolic acidosis with an elevated anion gap, ketosis, and hypoglycemia. Further evaluation reveals a markedly elevated propionic acid level due to defective conversion of propionyl-CoA to methylmalonyl-CoA. This patient is most likely unable to use which of the following amino acids for energy production?

A. Alanine (16%)
B. Aspartate (9%)
C. Glutamate (10%)
D. Lysine (13%)
E. Phenylalanine (15%)
✓ F. Valine (33%)

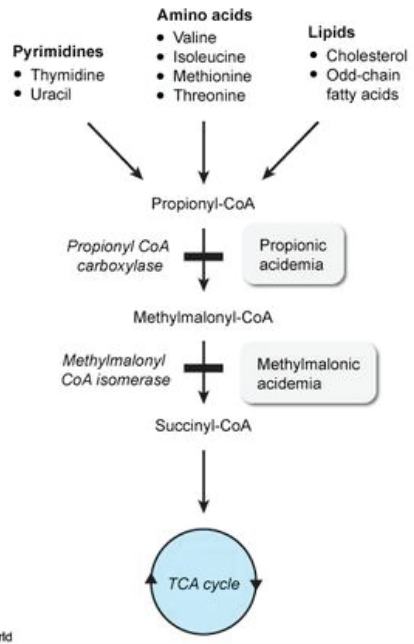
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Organic acidemia



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Catabolism of several essential amino acids (**valine**, **isoleucine**, **methionine**, and **threonine**) along with **odd-chain fatty acids** results in the generation of propionyl-CoA. Propionyl-CoA is subsequently converted to methylmalonyl-CoA in a reaction catalyzed by biotin-dependent propionyl-CoA carboxylase. Isomerization of methylmalonyl-CoA then generates succinyl-CoA, which enters the TCA cycle.

This patient's presentation is consistent with **propionic acidemia**, an autosomal recessive organic acidemia caused by congenital deficiency of propionyl-CoA carboxylase. This enzyme catalyzes the conversion of propionyl-CoA to methylmalonyl-CoA. In its absence, excess propionic acid accumulates in the bloodstream, causing **severe metabolic acidosis**. Hypoglycemia and ketosis frequently develop secondary to the acidosis. Affected patients present 1-2 weeks after birth with lethargy, poor feeding, vomiting, and hypotonia. Treatment involves starting a low-protein diet containing minimal amounts of valine, isoleucine, methionine, and threonine.

(Choice A) Alanine transaminase catalyzes the transfer of an amino group from alanine to α-ketoglutarate, generating pyruvate that can be used for gluconeogenesis.

(Choice B) Aspartate is a nonessential amino acid; it can be converted into oxaloacetate for use in the TCA cycle by aspartate transaminase.

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(Choice A) Alanine transaminase catalyzes the transfer of an amino group from alanine to α-ketoglutarate, generating pyruvate that can be used for gluconeogenesis.

(Choice B) Aspartate is a nonessential amino acid; it can be converted into oxaloacetate for use in the TCA cycle by aspartate transaminase.

(Choice C) Glutamate is deaminated by glutamate dehydrogenase to form the TCA cycle intermediate α-ketoglutarate.

(Choice D) Lysine and leucine are essential amino acids that are strictly ketogenic. They are metabolized into acetyl-CoA, which is a precursor for ketone bodies.

(Choice E) Phenylalanine is converted to tyrosine by the enzyme phenylalanine hydroxylase. Tyrosine is further converted into fumarate (TCA cycle intermediate) and acetoacetate (ketone body).

Educational objective:
Propionyl-CoA is derived from the metabolism of valine, isoleucine, methionine, threonine, and odd-chain fatty acids. Congenital deficiency of propionyl-CoA carboxylase, the enzyme responsible for the conversion of propionyl-CoA to methylmalonyl-CoA, leads to the development of propionic acidemia. The condition presents with lethargy, poor feeding, vomiting, and hypotonia 1-2 weeks after birth.

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A 52-year-old man is being evaluated in the emergency department for abdominal pain associated with watery diarrhea. His symptoms have been progressive over the last month. He says that he is depressed and often has difficulty remembering things. The patient has a 20-year history of alcohol abuse. On examination, he appears disheveled. A pigmented scaly skin rash is present in the malar distribution of his face, neck, and back of his hands. The rash has been present for several months and worsens on exposure to sunlight. It is determined that the patient's symptoms are secondary to lack of a specific nutrient. Activity of which of the following enzymes is most likely decreased in the patient as a result of this deficiency?

A. Citrate synthase
B. Hexokinase
C. Isocitrate dehydrogenase
D. Phosphoglycerate kinase
E. Succinate dehydrogenase

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A. ~~Citrate synthase~~ (7%)
B. ~~Hexokinase~~ (5%)
C. Isocitrate dehydrogenase (46%)
D. ~~Phosphoglycerate kinase~~ (8%)
E. Succinate dehydrogenase (31%)

Correct

46%

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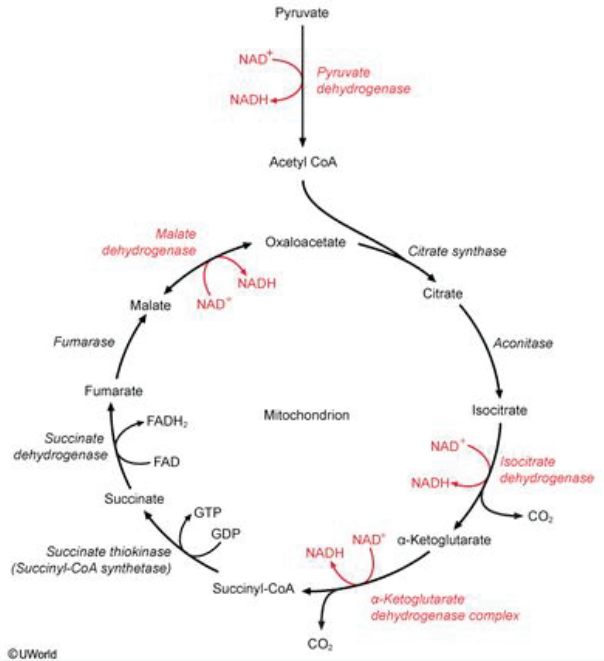
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Niacin dependent enzymes in TCA cycle



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This patient likely has **pellagra**, a disease characterized by photosensitive dermatitis, diarrhea, and dementia occurring secondary to **vitamin B_3 (niacin) deficiency**. In the United States, pellagra is seen predominantly in malnourished populations (eg, patients with alcoholism or GI malabsorption).

Niacin is a precursor for nicotinamide adenine dinucleotide (**NAD**) and nicotinamide adenine dinucleotide phosphate (**NADP**), two important **cofactors** for many **dehydrogenase** and **reductase enzymes**. NAD is required for catabolic reactions (eg, glycolysis, beta-oxidation) as well as cell signaling and DNA repair, whereas NADP is necessary for many anabolic reactions such as fatty acid and cholesterol synthesis. NAD is a key constituent of the citric acid cycle; it serves as a cofactor for isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, and malate dehydrogenase.

(Choice A) Citrate synthase is an enzyme of the citric acid cycle; it does not require NAD or NADP as a cofactor.

(Choices B and D) Hexokinase and phosphoglycerate kinase are enzymes used in glycolysis; they do not require NAD or NADP as cofactors.

(Choice E) Succinate dehydrogenase is an enzyme of the citric acid cycle; it catalyzes the conversion of succinate to fumarate using flavin adenine dinucleotide (FAD) as a cofactor.

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(Choices B and D) Hexokinase and phosphoglycerate kinase are enzymes used in glycolysis; they do not require NAD or NADP as cofactors.

(Choice E) Succinate dehydrogenase is an enzyme of the citric acid cycle; it catalyzes the conversion of succinate to fumarate using flavin adenine dinucleotide (FAD) as a cofactor.

Educational objective:
Niacin is a precursor for nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), two important cofactors for many dehydrogenase and reductase enzymes. Niacin deficiency results in pellagra (ie, diarrhea, dementia, and dermatitis).

References

- Pellagra: a non-eradicated old disease.

Biochemistry	Biochemistry (General Principles)	Niacin deficiency
Subject	System	Topic

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A research scientist is studying biochemical reactions that take place in the liver. He cultures hepatocytes in a growth media enriched with glutamate labeled with nitrogen isotopes. After some time, he finds that the nitrogen isotopes are transferred to oxaloacetate, forming aspartate in the process. Which of the following substances is most likely involved in this reaction?

- A. Biotin
- B. Folic acid
- C. Niacin
- D. Pyridoxine
- E. Riboflavin
- F. Thiamine

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A research scientist is studying biochemical reactions that take place in the liver. He cultures hepatocytes in a growth media enriched with glutamate labeled with nitrogen isotopes. After some time, he finds that the nitrogen isotopes are transferred to oxaloacetate, forming aspartate in the process. Which of the following substances is most likely involved in this reaction?

- A. Biotin (19%)
- B. ~~Folic acid~~ (2%)
- C. Niacin (11%)
- ✓ D. Pyridoxine (48%)
- E. Riboflavin (6%)
- F. ~~Thiamine~~ (12%)

Correct

48%
Answered correctly

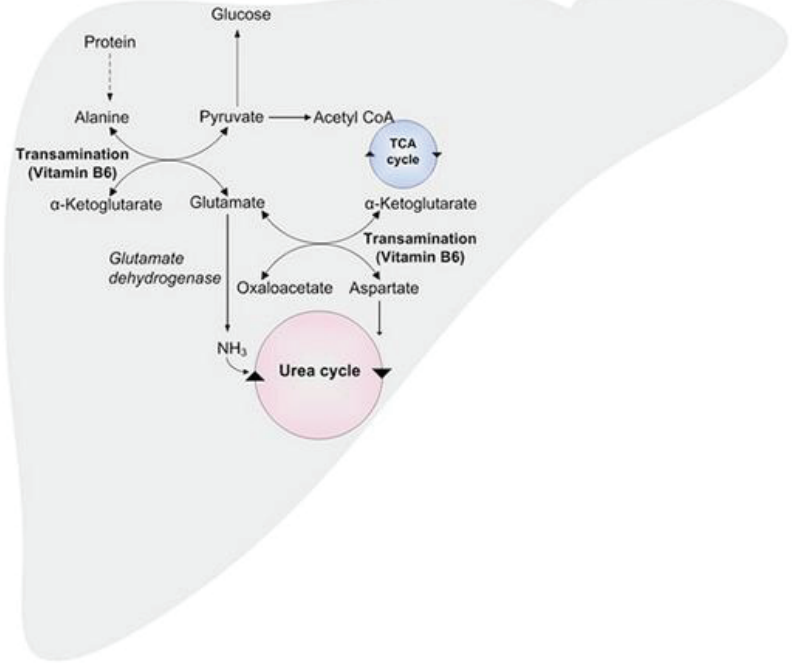
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Pyridoxine (vitamin B_6) is necessary for the transamination and decarboxylation of amino acids, for gluconeogenesis, and for other essential biochemical processes. **Transamination reactions** typically occur between an **amino acid** and an **α-keto acid**. The amino group is transferred to the α-keto acid from the amino acid, and the α-keto acid thereby becomes an amino acid. For example, glutamate (amino acid) reacts with oxaloacetate (α-keto acid) to form aspartate (the resulting amino acid) and α-ketoglutarate (the resulting α-keto acid).

Transaminases (aminotransferases) are the enzymes that catalyze transamination reactions, and pyridoxal phosphate (active vitamin B_6) serves as an essential cofactor for the transaminase.

(Choice A) Biotin (vitamin B_7) is a cofactor for all 4 carboxylase enzymes: pyruvate carboxylase, acetyl-CoA carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA-carboxylase.

(Choice B) Folic acid (vitamin B_9) is an essential cofactor in nucleic acid synthesis, and a deficiency of either folate or vitamin B_{12} results in megaloblastic anemia.

(Choice C) Many dehydrogenases use NAD+ and NADP+, which are formed from niacin. Niacin (vitamin B_3, or nicotinic acid) deficiency is known as pellagra and is classically associated with the 4 Ds: dermatitis,

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(Choice C) Many dehydrogenases use NAD+ and NADP+, which are formed from niacin. Niacin (vitamin B_3, or nicotinic acid) deficiency is known as pellagra and is classically associated with the 4 Ds: dermatitis, dementia, diarrhea, and, if untreated, death.

(Choice E) Riboflavin (vitamin B_2) is used in dehydrogenase reactions involving FMN and FAD.

(Choice F) Thiamine (vitamin B_1) serves as a coenzyme for a number of important dehydrogenase enzymes, including transketolase, α-ketoglutarate dehydrogenase, and pyruvate dehydrogenase.

Educational objective:
Transamination reactions typically occur between an amino acid and an α-keto acid. The amino group from the amino acid is transferred to the α-keto acid, and the α-keto acid in turn becomes an amino acid. Pyridoxal phosphate (active vitamin B_6) serves as a cofactor in amino acid transamination and decarboxylation reactions.

References

- Review: the role of coenzymes in clinical enzymology.
- An appreciation of Professor Alexander E. Braunstein. The discovery and scope of enzymatic transamination.

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An 8-year-old boy is brought to the emergency department due to vomiting and lethargy. The patient had been on an overnight hiking trip with his family. During the trip, the family lost their food pack while canoeing and had to hike back to their car. The child became weak and was carried for the last mile. None of the family has eaten for approximately 24 hours. On examination, the patient appears listless. Mild hepatomegaly is noted. Laboratory results are as follows:

Glucose	22 mg/dL
Acetoacetate	not detected
Aspartate aminotransferase	47 U/L
Alanine aminotransferase	53 U/L

The patient begins seizing shortly after arriving at the emergency department. Which of the following enzymes is most likely deficient in this patient?

A. Acetyl-CoA carboxylase

B. Acid alpha-glucosidase

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Glucose	22 mg/dL
Acetoacetate	not detected
Aspartate aminotransferase	47 U/L
Alanine aminotransferase	53 U/L

The patient begins seizing shortly after arriving at the emergency department. Which of the following enzymes is most likely deficient in this patient?

A. Acetyl-CoA carboxylase
B. Acid alpha-glucosidase
C. Acyl-CoA dehydrogenase
D. Glucose 6-phosphatase
E. Glycogen phosphorylase

Submit

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Glucose	22 mg/dL
Acetoacetate	not detected
Aspartate aminotransferase	47 U/L
Alanine aminotransferase	53 U/L

The patient begins seizing shortly after arriving at the emergency department. Which of the following enzymes is most likely deficient in this patient?

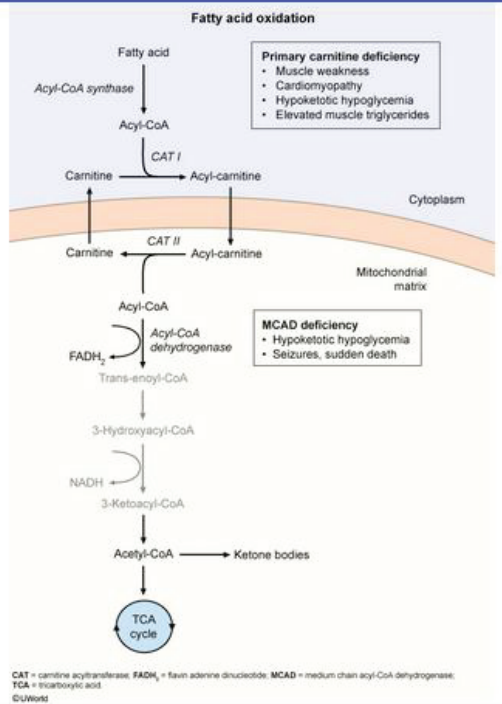
A. Acetyl-CoA carboxylase (15%)
B. Acid alpha-glucosidase (3%)
C. Acyl-CoA dehydrogenase (34%)
D. ~~Glucose 6-phosphatase~~ (25%)
E. ~~Glycogen phosphorylase~~ (21%)

Correct
34%
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CAT = carnitine acyltransferase; **$FADH_2$** = flavin adenine dinucleotide; **MCAD** = medium chain acyl-CoA dehydrogenase; **TCA** = tricarboxylic acid.

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This patient developed **hypoketotic hypoglycemia** after fasting, which is consistent with a **defect in fatty acid beta-oxidation** in the mitochondria. Beta-oxidation of fatty acids yields $FADH_2$ and NADH for ATP production and generates acetyl-CoA for use in the citric acid cycle or ketone body production. **Ketone bodies** are an important energy source during periods of fasting; adults generally require more than 1-2 days of fasting before ketone use becomes substantial, whereas children have limited glucose reserves and begin using ketone bodies after as little as 8-10 hours.

Impaired beta-oxidation can be caused by a variety of enzymatic defects, the most common of which is **medium chain acyl-CoA dehydrogenase deficiency**. Affected individuals may remain asymptomatic for long periods until they experience a **significant fast**, during which they are unable to oxidize fatty acids to maintain glucose and ketone body production. Classic manifestations include hypoketotic hypoglycemia (eg, undetectable acetoacetate level), mild hepatomegaly, and liver dysfunction. Because the resulting metabolic crisis can have severe consequences (eg, seizures, sudden infant death), fatty acid oxidation disorders are part of standard newborn screening.

Treatment of acyl-CoA dehydrogenase deficiency consists of prevention of fat catabolism. This means avoiding prolonged fasting as well as promptly supplying **glucose** during periods of illness.

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disorders are part of standard newborn screening.

Treatment of acyl-CoA dehydrogenase deficiency consists of prevention of fat catabolism. This means avoiding prolonged fasting as well as promptly supplying **glucose** during periods of illness.

(Choice A) Acetyl-CoA carboxylase is the rate-limiting enzyme that catalyzes the first step in fatty acid synthesis. Acetyl-CoA carboxylase is normally suppressed during prolonged fasting.

(Choices B, D, and E) Acid alpha-glucosidase, glucose 6-phosphatase, and glycogen phosphorylase are involved in glycogenolysis. Deficiency of any of these enzymes can lead to glycogen storage disease. However, patients with glycogen storage disease have normal fatty acid oxidation and produce ketones during periods of fasting.

Educational objective:
Impaired beta-oxidation of fatty acids causes hypoglycemia after prolonged fasting and insufficient levels of ketone bodies. Acyl-CoA dehydrogenase catalyzes the first step in the beta-oxidation pathway and is the most commonly deficient enzyme.

References

- Newborn screening for medium chain acyl CoA dehydrogenase deficiency.
- Ketone body transport in the human neonate and infant

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A 47-year-old homeless man comes to the emergency department due to a "pins-and-needles" sensation in his legs. He also has painful lesions on his lips and corners of his mouth. He has had no loss of consciousness, nausea, vomiting, or diplopia. The patient drinks alcohol heavily on a daily basis and has a history of intravenous heroin use. On physical examination, he appears unkempt and ill appearing. Temperature is 36.8 C (98.2 F), blood pressure is 146/90 mm Hg, and pulse is 106/min. He has glossitis and angular stomatitis. Abdominal examination reveals hepatomegaly. Laboratory evaluation shows very low urinary riboflavin excretion. Activity of which of the following enzymes is most likely directly impaired in this patient?

A. Fumarase
B. Glucose-6-phosphate dehydrogenase
C. HMG-CoA reductase
D. Isocitrate dehydrogenase
E. Malate dehydrogenase
F. Succinate dehydrogenase

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A. Fumarase
B. Glucose-6-phosphate dehydrogenase
C. HMG-CoA reductase
D. Isocitrate dehydrogenase
E. Malate dehydrogenase
F. Succinate dehydrogenase
G. Succinate thiokinase

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A. ~~Fumarase~~ (7%)
B. Glucose-6-phosphate dehydrogenase (7%)
C. ~~HMG-CoA reductase~~ (6%)
D. ~~Isocitrate dehydrogenase~~ (14%)
E. ~~Malate dehydrogenase~~ (9%)
F. Succinate dehydrogenase (50%)
G. ~~Succinate thiokinase~~ (4%)

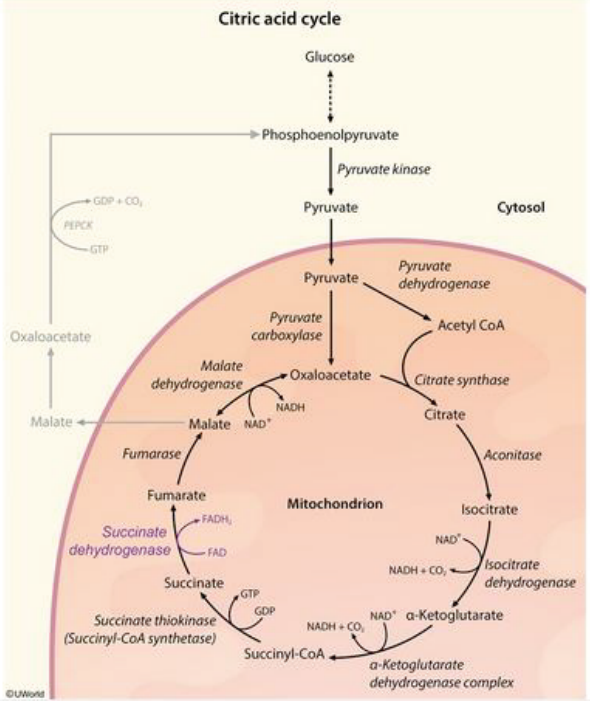
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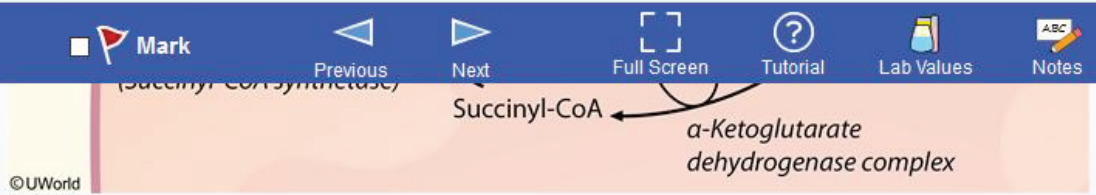
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This patient's low urinary riboflavin excretion suggests a significant deficiency in riboflavin intake. Symptomatic **riboflavin deficiency** is rare in the United States but can be seen in chronic alcoholics and the severely malnourished. Clinical manifestations include angular stomatitis, cheilitis, glossitis, seborrheic dermatitis, eye changes (eg, keratitis, corneal neovascularization), and anemia.

The **riboflavin** (vitamin B_2)-containing coenzymes are key constituents of the **electron transport chain**. Typically, riboflavin is first phosphorylated to become flavin mononucleotide (FMN), which can then be integrated into a coenzyme-flavin complex or further phosphorylated to flavin adenine dinucleotide (FAD). FMN and FAD participate as coenzymes in numerous reduction-oxidation reactions and are converted into reduced, energy-carrying states ($FMNH_2$ and $FADH_2$) through the acceptance of electrons.

FMN serves as a component of complex I, whereas FAD functions as a component of **succinate dehydrogenase** (complex II). Complex II participates in both the electron transport chain and tricarboxylic acid (TCA) cycle. During the TCA cycle, succinate dehydrogenase converts succinate to fumarate and transfers electrons to coenzyme Q (ubiquinone) via FAD. Complex II also accepts electrons from other sources of $FADH_2$, such as fatty acid oxidation.

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sources of $FADH_2$, such as fatty acid oxidation.

(Choices A, D, E, and G) Isocitrate dehydrogenase, succinate thiokinase, malate dehydrogenase, and fumarase are enzymes that participate in the TCA cycle but do not use FAD or FMN as cofactors.

(Choice B) Reduced glutathione is an antioxidant that minimizes oxidative damage in many cells. Glutathione reductase regenerates reduced glutathione using nicotinamide adenine dinucleotide phosphate (NADPH) as an electron donor and FAD as a cofactor. Although glucose-6-phosphate dehydrogenase (G6PD) is the rate-limiting enzyme in the pentose phosphate pathway and supplies the necessary NADPH, it does not use FAD as a cofactor.

(Choice C) HMG-CoA reductase is the rate-limiting enzyme in the cholesterol synthesis pathway. FMN and FAD are not used as cofactors.

Educational objective:
Riboflavin is a precursor of the coenzymes FMN and FAD. FAD participates in the tricarboxylic acid cycle and electron transport chain by acting as an electron acceptor for succinate dehydrogenase (complex II), which converts succinate into fumarate.

References

- Update on clinical aspects and treatment of selected vitamin-responsive disorders II (riboflavin and CoQ

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A 1-day-old boy is diagnosed with hyperphenylalaninemia by newborn screening. He is placed on a special phenylalanine-restricted diet with tyrosine supplementation. The parents are extensively counseled on the boy's condition and informed of the necessary dietary restrictions. They are also instructed to return to his physician for regular follow-up visits. Several months later, laboratory test results indicate that the infant has a normal serum phenylalanine level. Careful examination, however, reveals some neurological abnormalities, including axial hypotonia and microcephaly. Further workup is notable for elevated prolactin, and his physician suspects a cofactor deficiency. Which of the following enzymes is most likely deficient in this patient?

A. Dihydrobiopterin reductase
B. Dopamine β-hydroxylase
C. Phenylalanine hydroxylase
D. Phenylethanolamine N-methyltransferase
E. Tyrosinase

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- A. Dihydrobiopterin reductase (50%)
- B. Dopamine β-hydroxylase (17%)
- C. Phenylalanine hydroxylase (14%)
- D. Phenylethanolamine N-methyltransferase (7%)
- E. Tyrosinase (10%)

Correct

50%
Answered correctly

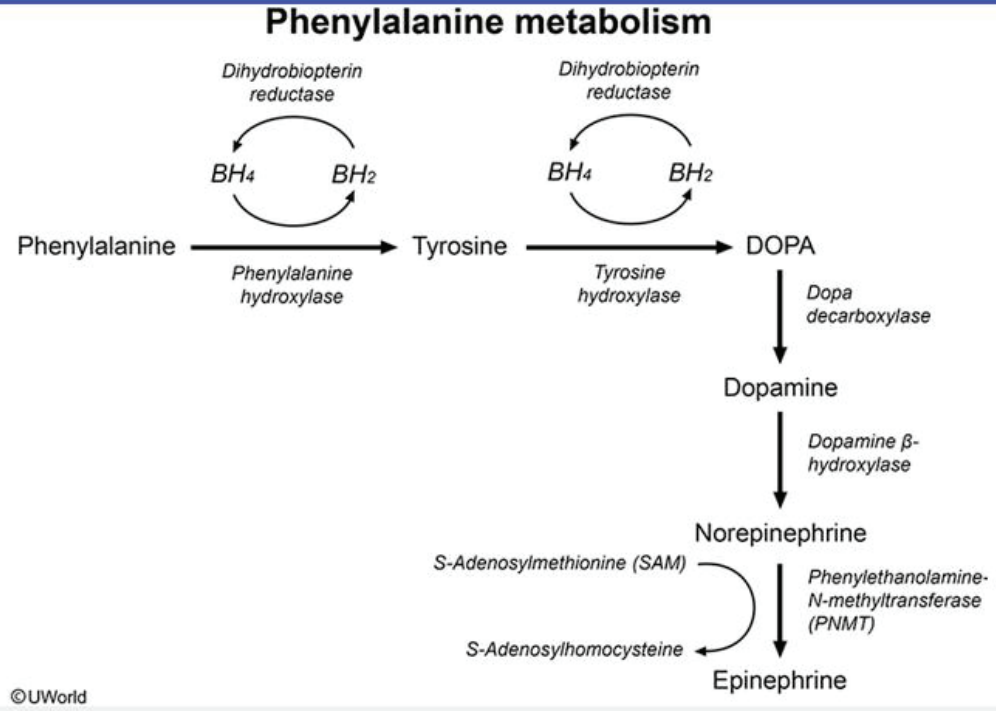
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This patient with phenylketonuria (PKU) most likely has a deficiency of dihydrobiopterin reductase (reduces BH_2 to BH_4) based on the combination of **hyperphenylalaninemia** and **elevated prolactin**. Phenylalanine is converted to tyrosine by phenylalanine hydroxylase using BH_4 as a cofactor. Tyrosine is converted to DOPA via the enzyme tyrosine hydroxylase, which also uses BH_4 as a cofactor. Once DOPA is synthesized, it is decarboxylated to dopamine by DOPA decarboxylase. Dopamine ultimately serves as the precursor molecule to the catecholamines epinephrine and norepinephrine.

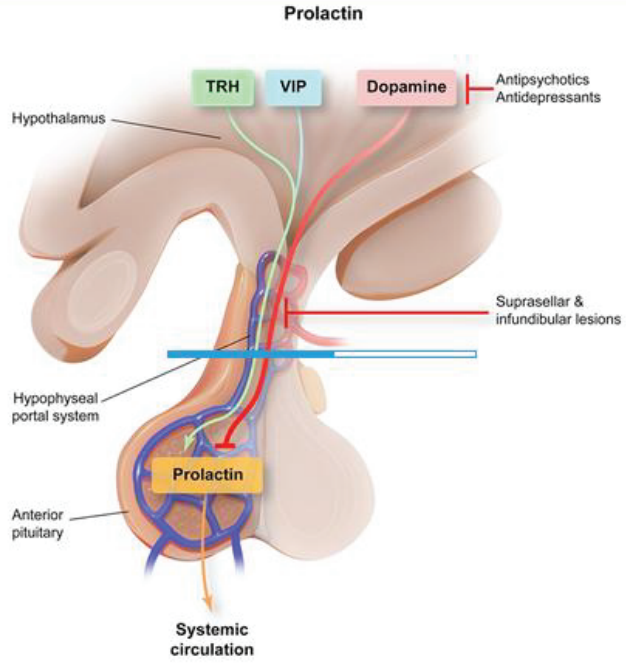
In classic PKU, supplementation of tyrosine allows for normal catecholamine production due to intact function of tyrosine hydroxylase. However, deficiency of **dihydrobiopterin reductase** results in both **hyperphenylalaninemia** from impaired phenylalanine hydroxylase activity and **low dopamine** levels from impaired tyrosine hydroxylase activity. Although phenylalanine levels can be controlled by dietary restriction, downstream deficiencies of neurotransmitters (eg, dopamine, norepinephrine, epinephrine, serotonin) lead to progressive neurologic deterioration in these patients. Normally, dopamine from the tuberoinfundibular system tonically inhibits prolactin release. Decreased BH_4 causes lower levels of dopamine, resulting in **increased prolactin** levels.

(Choice B) The enzyme dopamine β-hydroxylase catalyzes the biosynthesis of norepinephrine from dopamine. It does not use BH_4 as a cofactor.

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(Choice B) The enzyme dopamine β-hydroxylase catalyzes the biosynthesis of norepinephrine from dopamine. It does not use BH_4 as a cofactor.

(Choice C) Phenylalanine hydroxylase deficiency is the most common cause of PKU. This patient's phenylalanine levels have normalized with dietary therapy, but he has low dopamine levels (as indicated by elevated prolactin). Patients with classic PKU or phenylalanine hydroxylase deficiency do not have any difficulty producing dopamine with adequate levels of dietary tyrosine.

(Choice D) Phenylethanolamine N-methyltransferase (PNMT) converts norepinephrine to epinephrine. It requires S-adenosyl-methionine (SAM) as a cofactor.

(Choice E) Tyrosinase deficiency causes albinism, characterized by a lack of pigment in skin and hair due to absent melanin production. Melanin is synthesized in melanocytes from tyrosine by tyrosinase.

Educational objective:
Dihydrobiopterin reductase deficiency results in impaired tetrahydrobiopterin (BH_4) levels. BH_4 is an important cofactor for both phenylalanine hydroxylase and tyrosine hydroxylase. Although phenylalanine levels can be corrected with dietary restriction, downstream deficiencies of dopamine, norepinephrine, epinephrine, and serotonin lead to progressive neurologic deterioration.

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Biologists investigating the morphologic changes associated with reversible cellular injury perform a procedure on anesthetized mice to assess the effects of transient hepatic ischemia. During the experiment, they clamp the hepatic artery and obtain liver biopsy samples at varying intervals. The samples are then examined by electron microscopy. Cells that are exposed to longer ischemic periods are found to have reduced numbers of ribosomes attached to the endoplasmic reticulum. This structural change is most likely to impair which of the following cellular functions?

A. ATP production
B. Drug detoxification
C. Synthesis of cell membrane proteins
D. Synthesis of cytosolic proteins
E. Synthesis of steroid hormones

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A. ATP production (3%)
B. Drug detoxification (3%)
C. Synthesis of cell membrane proteins (64%)
D. Synthesis of cytosolic proteins (24%)
E. Synthesis of steroid hormones (4%)

Correct

64%
Answered correctly

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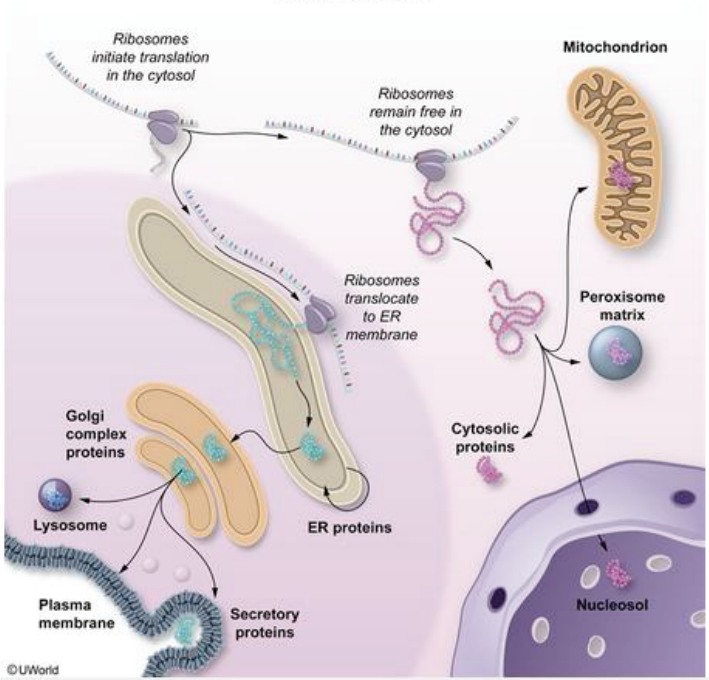
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Protein targeting



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Ribosomes are cellular organelles that synthesize proteins. Each ribosome consists of 2 subunits. The small ribosomal 40S subunit is responsible for binding mRNA (the protein synthesis template) and tRNA (carries amino acids). The larger 60S subunit contains peptidyl transferase, the enzyme that catalyzes peptide bond formation between amino acids. All ribosomes begin protein translation in the cytoplasm, but some translocate to the rough endoplasmic reticulum (RER) during protein synthesis depending on the protein's target destination.

- **Free ribosomes** remain floating in the cytosol throughout protein synthesis. They are responsible for translating proteins found within the cytosol, nucleosol, peroxisome matrix, and nuclear-encoded mitochondrial proteins **(Choice D)**.
- **Attached ribosomes** bind to the RER after protein translation begins. They synthesize most secretory proteins, the integral membrane proteins of the nucleus and cell membrane, and proteins within the ER, Golgi network, and lysosomes.

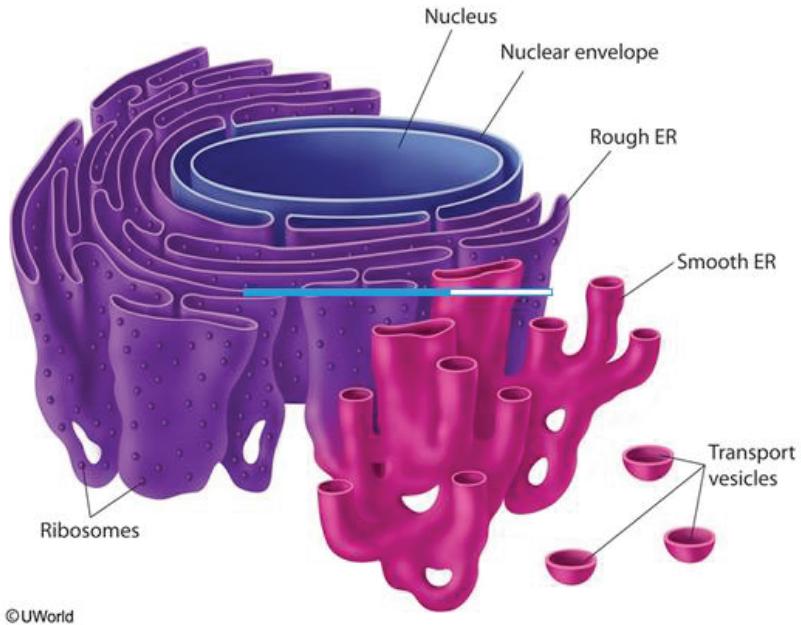
The RER is particularly well developed in protein-secreting cells (eg, pancreatic and plasma cells). Ribosomes attach to the RER via the **translocon**, a protein complex containing ribophorins that bind the large 60S subunit.

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Rough & smooth endoplasmic reticulum



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large 60S subunit

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large 60S subunit.

(Choice A) ATP is produced in the cytosol during glycolysis and in the mitochondria during oxidative phosphorylation. The proteins in both of these cellular compartments are synthesized by free ribosomes in the cytosol.

(Choices B and E) Steroid hormone synthesis and drug detoxification are performed by various proteins found within the smooth ER (SER). The SER does not bind to ribosomes as it lacks the translocon complex.

Educational objective:
The rough endoplasmic reticulum (RER) is covered with ribosomes and is involved in the transfer of proteins to the cell membrane and extracellular space. The RER is well developed in protein-secreting cells. The smooth ER lacks surface ribosomes and functions in lipid synthesis, carbohydrate metabolism, and detoxification of harmful substances.

Biochemistry	Biochemistry (General Principles)	Protein synthesis
Subject	System	Topic

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A 4-month-old boy is brought to the office for his first visit since arriving in the United States. The patient was recently adopted, and his adoptive mother says the boy is tremulous compared to her biological children. Over the past week, the boy has also had episodes of upward eye deviation and bilateral arm and leg shaking for approximately 2 minutes at a time. Biological family history is not available. His temperature is 36.7 C (98.1 F), blood pressure is 90/40 mm Hg, pulse is 120/min, and respirations are 30/min. Examination shows a fair-skinned infant with blue eyes and a musty body odor. Which of the following amino acids is most likely essential in this patient?

A. Cysteine
B. Isoleucine
C. Leucine
D. Phenylalanine
E. Tyrosine
F. Valine

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was recently adopted, and his adoptive mother says the boy is tremulous compared to her biological children. Over the past week, the boy has also had episodes of upward eye deviation and bilateral arm and leg shaking for approximately 2 minutes at a time. Biological family history is not available. His temperature is 36.7 C (98.1 F), blood pressure is 90/40 mm Hg, pulse is 120/min, and respirations are 30/min. Examination shows a fair-skinned infant with blue eyes and a musty body odor. Which of the following amino acids is most likely essential in this patient?

A. Cysteine (4%)
B. Isoleucine (0%)
C. Leucine (1%)
D. Phenylalanine (17%)
E. Tyrosine (74%)
F. Valine (0%)

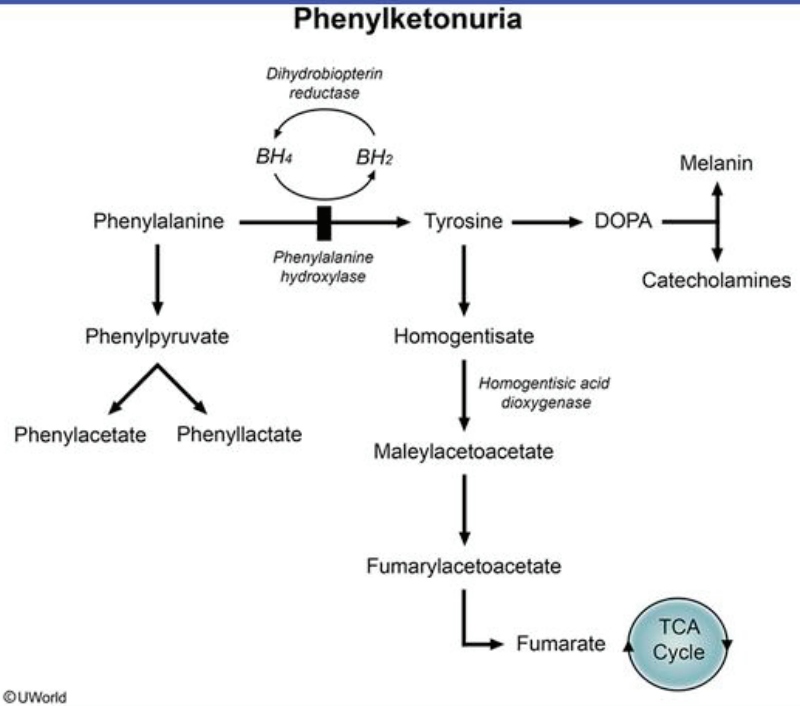
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This patient's clinical presentation suggests phenylketonuria (PKU). Classic PKU (the most common form) occurs most frequently in persons of Scandinavian descent. Individuals who are homozygous for this **autosomal recessive** disorder have a severe **deficiency** of **phenylalanine hydroxylase**, the enzyme responsible for conversion of phenylalanine to tyrosine. Tyrosine becomes an essential amino acid in these patients as it cannot be synthesized from phenylalanine, although most patients receive adequate amounts in their diet and do not require supplementation. Furthermore, the excess phenylalanine inhibits tyrosinase, which normally results in the downstream production of melanin. The lack of melanin causes the **fair complexion** seen in this patient.

Although development is initially normal, most untreated patients develop **intellectual disability** by age 6 months. Other classic findings include **seizures**, eczema, light hair/skin pigmentation, and a "**musty**," odor. However, cognitive impairment can be lessened by early detection (newborn screening) and **restriction of phenylalanine intake**.

(Choice A) Cystinuria is due to impaired transport of renal cystine (a homodimer of cysteine), which leads to cystine renal stone formation. Clinical manifestations typically include flank pain, hematuria, and possible stone passage in children or adolescents.

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(Choice A) Cystinuria is due to impaired transport of renal cystine (a homodimer of cysteine), which leads to cystine renal stone formation. Clinical manifestations typically include flank pain, hematuria, and possible stone passage in children or adolescents.

(Choices B, C, and F) The branched-chain amino acids (leucine, isoleucine, valine) are elevated in maple syrup urine disease, an amino acid disorder marked by deficiency of branched-chain alpha-ketoacid dehydrogenase complex. Buildup of the branched-chain amino acids and their metabolites is toxic, leading to feeding difficulties, seizures, cerebral edema, and a sweet odor of the urine.

(Choice D) Phenylalanine levels are significantly elevated in PKU, leading to neurologic defects. Therapy depends on dietary restriction of phenylalanine.

Educational objective:

Phenylketonuria (PKU) results from an inability to convert phenylalanine to tyrosine by the phenylalanine hydroxylase system, making tyrosine an essential amino acid in these patients. Classic clinical features of untreated PKU include intellectual disability, seizures, light pigmentation, and a "musty" odor.

References

- Phenylalanine hydroxylase deficiency: diagnosis and management guideline.

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Researchers lyse human cells and isolate a specific messenger RNA template using gel electrophoresis. Reverse transcription polymerase chain reaction is then used to synthesize complementary DNA (cDNA) from the RNA template. Next, the cDNA is modified into an expression vector containing an optimized bacterial promoter, ribosomal binding site, and terminator sequence. After insertion of the vector into appropriate bacterial hosts, the transformed bacteria are cultured in a bioreactor and produce large quantities of a protein containing a domain that binds to a specific DNA sequence. This protein is most likely the receptor for which of the following hormones?

A. Glucagon
B. Growth hormone
C. Insulin
D. Insulin-like growth factor
E. Parathyroid hormone
F. Progesterone

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Reverse transcription polymerase chain reaction is then used to synthesize complementary DNA (cDNA) from the RNA template. Next, the cDNA is modified into an expression vector containing an optimized bacterial promoter, ribosomal binding site, and terminator sequence. After insertion of the vector into appropriate bacterial hosts, the transformed bacteria are cultured in a bioreactor and produce large quantities of a protein containing a domain that binds to a specific DNA sequence. This protein is most likely the receptor for which of the following hormones?

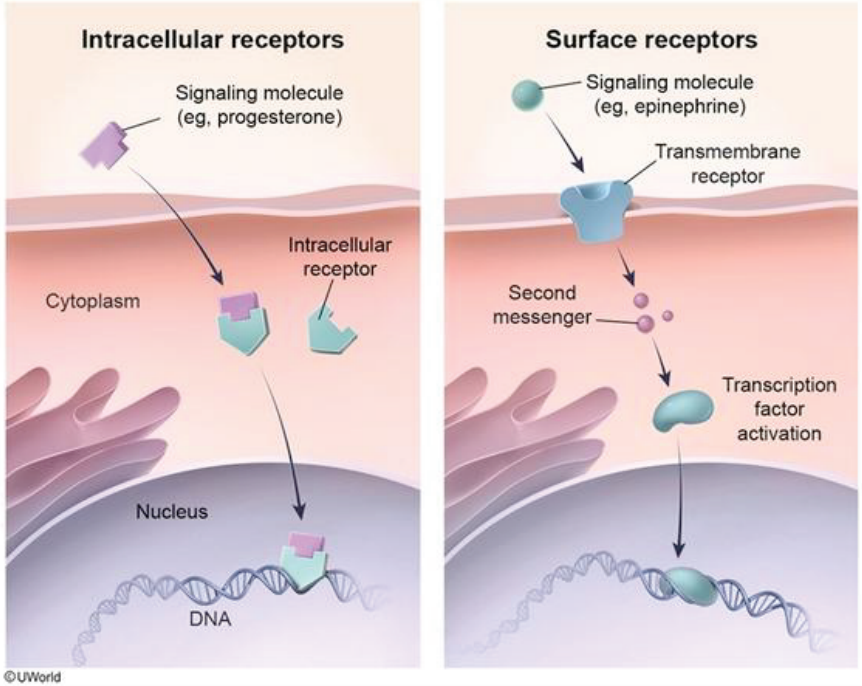
A. ~~Glucagon~~ (2%)
B. ~~Growth hormone~~ (12%)
C. ~~Insulin~~ (11%)
D. ~~Insulin-like growth factor~~ (14%)
E. ~~Parathyroid hormone~~ (2%)
✓ F. Progesterone (56%)

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56%
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Prokaryotes and eukaryotes use divergent cellular machinery for protein synthesis and require different signaling sequences for efficient transcription and translation. Expression cloning is a type of DNA cloning where the signals necessary for optimal protein expression are included in the DNA vector. In this example, **eukaryotic complementary DNA** (containing the **coding sequence** for the protein of interest) is modified with **prokaryotic promoter** sequences (eg, the Pribnow box, −35 sequence) and a **ribosomal binding site** (Shine-Dalgarno sequence). The vector is then incorporated into a suitable bacterial host (eg, *Escherichia coli*) and subsequently transcribed and translated into protein.

The protein produced in the bioreactor contains a **DNA-binding domain**. DNA-binding proteins are a diverse group that include **transcription factors** (Myc, CREB), **steroid** receptors (cortisol, aldosterone, progesterone), **thyroid hormone** receptor, **fat-soluble vitamin receptors** (vitamin D, retinoic acid), and DNA transcription and replication proteins.

Of the choices listed, only the **progesterone receptor** can bind to DNA. The receptors for most steroid hormones, including progesterone, are located in the cytoplasm and translocate to the nucleus upon ligand binding. In contrast, receptors for thyroid hormone and vitamins A and D are located within the nucleus at all times. Following activation by ligand binding, both receptor types attach to DNA at hormone response

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all times. Following activation by ligand binding, both receptor types attach to DNA at hormone response elements located in the promoter region of target genes to alter gene transcription.

(Choices A and E) Parathyroid hormone and glucagon act on Gs protein-coupled receptors found on the cell membrane. Binding their respective ligands subsequently activates adenylyl cyclase and increases intracellular cyclic AMP concentration.

(Choice B) Growth hormone receptor is a membrane-bound receptor that works via activating the JAK-STAT pathway.

(Choices C and D) The receptors for insulin-like growth factor-1 (IGF-1) and insulin are structurally similar and located at the cell membrane. The intracellular domains of these receptors have intrinsic tyrosine kinase activity, which is activated on ligand binding. Autophosphorylation of the tyrosine residues on the intracellular part of the receptors then triggers downstream signaling.

Educational objective:
DNA-binding proteins include transcription factors (Myc, CREB), steroid receptors (cortisol, aldosterone, progesterone), thyroid hormone receptor, fat-soluble vitamin receptors (vitamin D, retinoic acid), and DNA transcription and replication proteins.

References

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Molecular biologists perform a series of experiments to characterize the electrophysiologic properties of human muscle cells. The resting membrane potential for an isolated muscle cell is determined to be -70 mV. The equilibrium potentials for important ions under normal physiologic conditions are as follows:

E_{Na} = + 60 mV

E_{K} = - 90 mV

E_{Cl} = - 75 mV

E_{Ca} = + 125 mV

E_{Mg} = 0 mV

If physiologic conditions are maintained, which of the following ions would most likely flow out of the cell after opening of their respective ion channels?

A. Magnesium and calcium

B. Magnesium and chloride

C. Potassium and chloride

D. Potassium only

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E_{Na} = + 60 mV

E_{K} = - 90 mV

E_{Cl} = - 75 mV

E_{Ca} = + 125 mV

E_{Mg} = 0 mV

If physiologic conditions are maintained, which of the following ions would most likely flow out of the cell after opening of their respective ion channels?

A. Magnesium and calcium

B. Magnesium and chloride

C. Potassium and chloride

D. Potassium only

E. Sodium and calcium

Submit

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E_K = - 90 mV

E_{Cl} = - 75 mV

E_{Ca} = + 125 mV

E_{Mg} = 0 mV

If physiologic conditions are maintained, which of the following ions would most likely flow out of the cell after opening of their respective ion channels?

A. Magnesium and calcium (1%)

B. Magnesium and chloride (1%)

C. Potassium and chloride (42%)

D. Potassium only (42%)

E. Sodium and calcium (12%)

Correct

42%

58 secs

10/27/2020

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Equilibration movements of charged ions under physiologic conditions

Ion	Charge	Major location	Equilibrium potential	Equilibration movement at -70 mV
Sodium	Positive	Extracellular	+ 60 mV	Extracellular gradient drives Na^+ into cell, making membrane potential more positive **(Choice E)**
Potassium	Positive	Intracellular	- 90 mV	Intracellular gradient drives K^+ out of cell, making membrane potential more negative
Chloride	Negative	Extracellular	- 75 mV	Extracellular gradient drives Cl^- into cell, making membrane potential more negative **(Choices B and C)**
Calcium	Positive	Extracellular	+ 125 mV	Extracellular gradient drives Ca^{2+} into cell, making membrane potential more positive **(Choice A)**

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Na^+, K^+, and Cl^- are the main ions that determine the electrical potential difference (voltage) across a membrane (**membrane potential**). Under normal physiologic conditions, there is a low concentration of Na^+ and Cl^- in the cell and high concentration of K^+ in the cytoplasm. Conversely, the extracellular space has a high concentration of Na^+ and Cl^- ions and low concentration of K^+ ions.

Because intracellular K^+ concentration is much greater than its extracellular concentration, opening of cellular potassium channels leads to K^+ efflux from the cell along the K^+ concentration gradient. Within the cell, the positive charge of the K^+ ions is normally neutralized by the negative charge of intracellular anions (eg, phosphates and proteins) that are trapped in the cell. As K^+ ions leave the cell, negatively charged anions accumulate along the inner side of the cell membrane. This continually increasing negative charge attracts the positively charged K^+ ions back into the cell. When the difference in concentration (diffusion potential) of K^+ inside and outside the cell is large, the efflux of K^+ ions will continue despite the increasing negative charge. At a certain point, however, the negative intracellular charge (electrical potential) of the membrane becomes large enough that the number of K^+ ions it attracts into the cell equals the number of K^+ ions that leave the cell along the concentration gradient. The electrical potential difference that moves K^+ ions into the cell at the same rate as they leave the cell along the concentration gradient is called the

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anions accumulate along the inner side of the cell membrane. This continually increasing negative charge attracts the positively charged K^+ ions back into the cell. When the difference in concentration (diffusion potential) of K^+ inside and outside the cell is large, the efflux of K^+ ions will continue despite the increasing negative charge. At a certain point, however, the negative intracellular charge (electrical potential) of the membrane becomes large enough that the number of K^+ ions it attracts into the cell equals the number of K^+ ions that leave the cell along the concentration gradient. The electrical potential difference that moves K^+ ions into the cell at the same rate as they leave the cell along the concentration gradient is called the **equilibrium potential**.

Educational objective:

When a specific ion channel opens, the respective ions will flow across the membrane in a direction that brings the resting membrane potential closer to that ion's equilibrium potential.

References

- Generation of resting membrane potential.

Biochemistry	Biochemistry (General Principles)	Resting membrane potential and action potential
Subject	System	Topic

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A 69-year-old woman with Alzheimer disease is brought to the emergency department after getting lost while taking a walk in her neighborhood. Her son has been unable to contact the patient for the last 2 days, and today the police found her wandering in a park. The patient says that she drank water from a park fountain but has not had anything to eat for over 24 hours. On physical examination, she is mildly confused with dry mucous membranes. Laboratory studies show a blood glucose level of 92 mg/dL. Which of the following hormones binds to an intracellular receptor to help maintain this patient's laboratory findings within the normal range?

A. Cortisol
B. Epinephrine
C. Glucagon
D. Growth hormone
E. Insulin
F. Norepinephrine

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while taking a walk in her neighborhood. Her son has been unable to contact the patient for the last 2 days, and today the police found her wandering in a park. The patient says that she drank water from a park fountain but has not had anything to eat for over 24 hours. On physical examination, she is mildly confused with dry mucous membranes. Laboratory studies show a blood glucose level of 92 mg/dL. Which of the following hormones binds to an intracellular receptor to help maintain this patient's laboratory findings within the normal range?

A. Cortisol (64%)
B. ~~Epinephrine~~ (3%)
C. ~~Glucagon~~ (26%)
D. ~~Growth hormone~~ (2%)
E. ~~Insulin~~ (2%)
F. ~~Norepinephrine~~ (0%)

Omitted
Correct answer

64%

22 secs

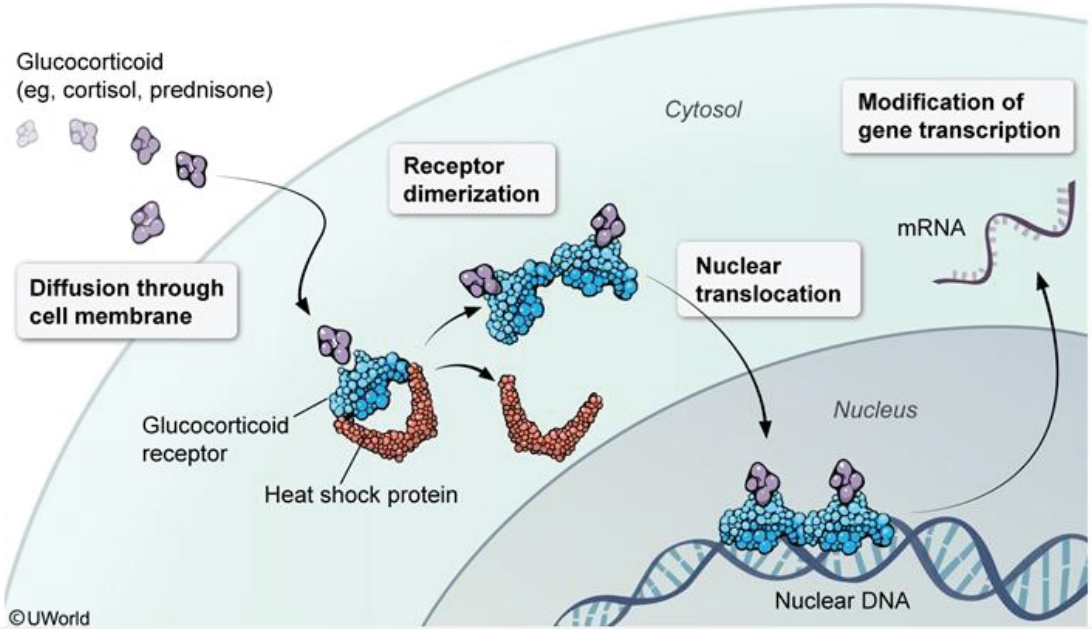
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Exhibit Display

Glucocorticoid mechanism of action



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This patient has experienced a prolonged fast, but her blood glucose level is normal. As blood glucose levels fall in the fasting state, hypoglycemia is prevented due to suppression of insulin secretion and activation of counterregulatory hormones. **Glucagon** is the primary hormone secreted acutely in response to falling glucose levels; it stimulates hepatic glycogenolysis and gluconeogenesis. Concurrently, **epinephrine** further stimulates glycogenolysis and gluconeogenesis, increases the release of gluconeogenic substrates from muscle and fat, and limits glucose utilization by some insulin-sensitive peripheral tissues.

As the fast continues, secretion of cortisol and growth hormone increases; these hormones attenuate hypoglycemia by altering transcription of key enzymes. In the inactivated state, **intracellular cortisol receptors** are found in the **cytoplasm** in association with heat shock proteins. Binding of cortisol to the carboxy terminal portion of the receptor causes the release of the heat shock proteins and allows receptor dimerization. The activated homodimers are then **transported to the nucleus**, where they control gene expression by binding to hormone-responsive DNA elements in the promoter region of target genes. Cortisol **increases transcription** of **gluconeogenic enzymes** as well as those involved in lipolysis and proteolysis.

(Choices B, C, and F) Catecholamines (eg, epinephrine, norepinephrine) and glucagon attenuate

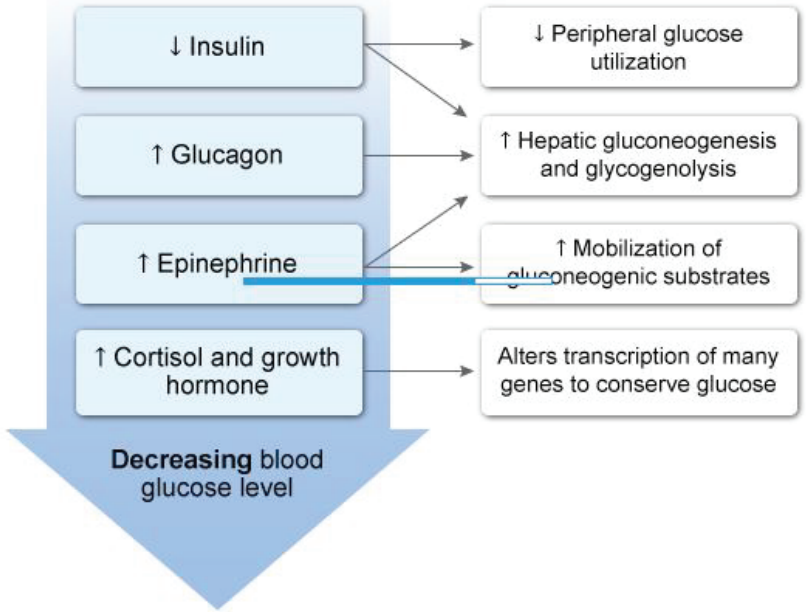
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Physiologic defense against hypoglycemia



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(Choices B, C, and F) Catecholamines (eg, epinephrine, norepinephrine) and glucagon attenuate

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(Choices B, C, and F) Catecholamines (eg, epinephrine, norepinephrine) and glucagon attenuate hypoglycemia. However, they exert their metabolic effects via *extracellular*, transmembrane, G protein–coupled receptors that activate adenyl cyclase and increase cyclic AMP production.

(Choice D) Growth hormone acts via an *extracellular*, transmembrane receptor that activates a JAK-STAT pathway. Growth hormone antagonizes insulin action, increases gluconeogenesis, and promotes lipolysis (provides gluconeogenic substrates).

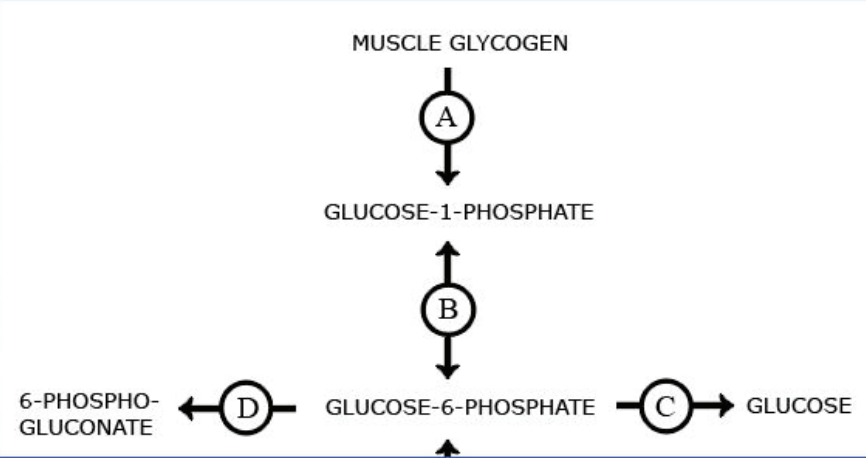
(Choice E) In addition to the production of counterregulatory hormones, the inhibition of insulin release from pancreatic beta cells plays a primary role in preventing hypoglycemia during fasting. However, insulin acts on a *extracellular* transmembrane receptor with intrinsic tyrosine kinase activity.

Educational objective:
In a fasting state, glucagon and epinephrine bind to transmembrane receptors and prevent hypoglycemia by increasing hepatic glycogenolysis and gluconeogenesis. Prolonged fasting increases the secretion of cortisol, a steroid hormone that binds to an intracellular receptor and acts to increase transcription of enzymes involved in gluconeogenesis, lipolysis, and proteolysis.

Biochemistry	Biochemistry (General Principles)	Gluconeogenesis
Subject	System	Topic

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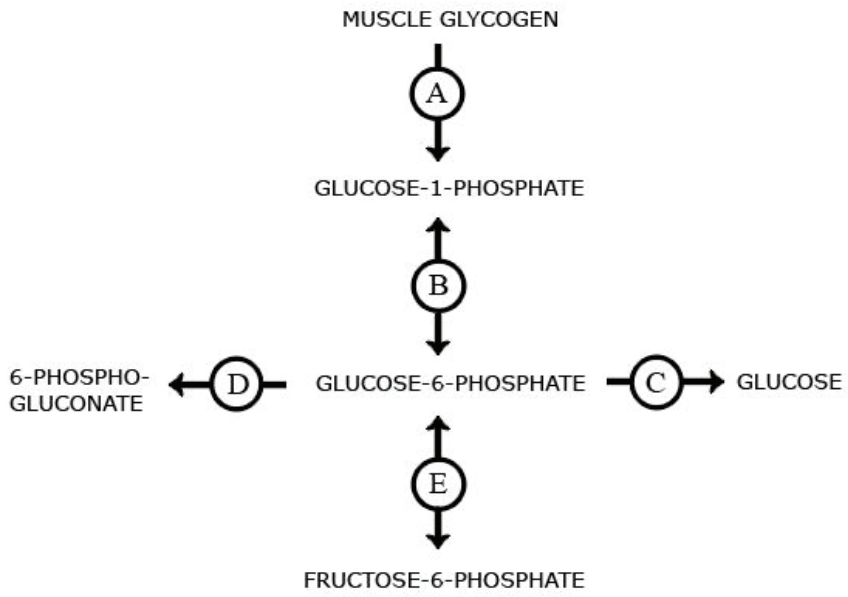
A 15-year-old boy is being evaluated for poor exercise endurance. He recently started weightlifting with some of his friends and is disappointed that he is "the weakest one by far." He says he tries as hard as possible, but his "arms feel like jelly after just a few repetitions." The patient also says he sometimes experiences severe muscle cramping and urine discoloration after periods of intense straining. Further evaluation reveals that his exercise tolerance can be greatly improved by drinking an oral glucose solution before beginning a strenuous activity. This patient is most likely deficient in an enzyme that catalyzes which of the following conversions?



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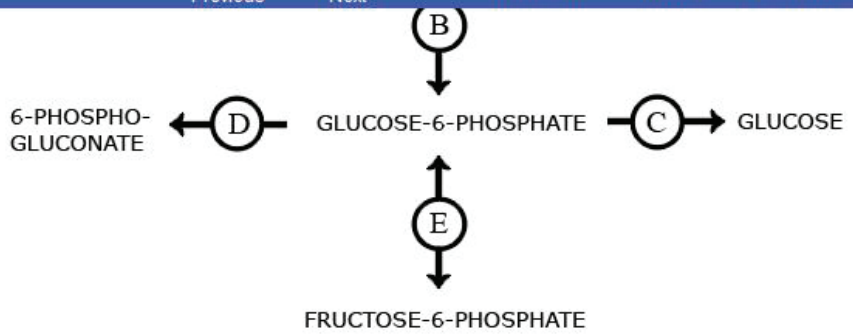
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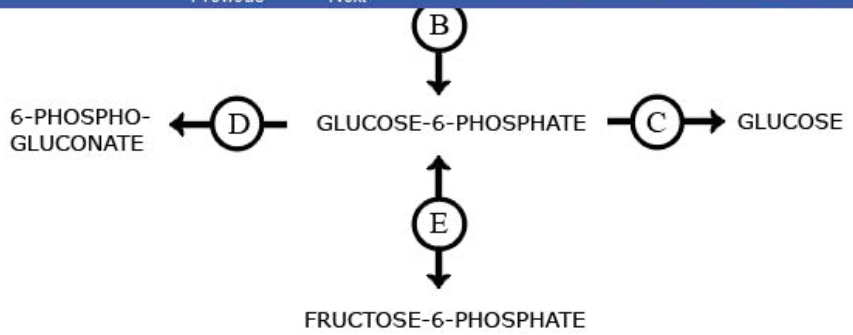
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- A.A
- B.B
- C.C
- D.D
- E.E

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- A.A (67%)
- B.B (9%)
- C.C (18%)
- D.D (1%)
- E.E (1%)

Correct

67%

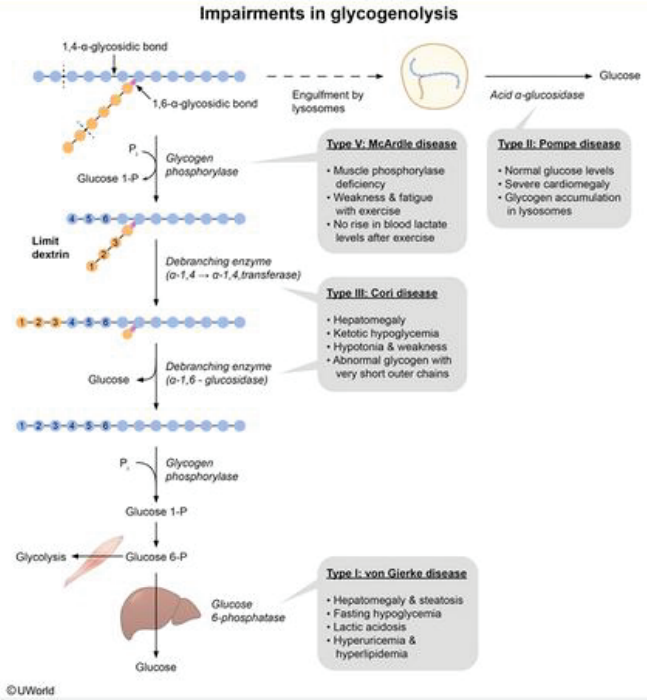
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This patient most likely has **McArdle disease** (glycogen storage disease type V). This condition is caused by deficiency of **myophosphorylase**, an isoenzyme of glycogen phosphorylase present in muscle tissue. Deficiency of this enzyme leads to decreased breakdown of glycogen during exercise, resulting in **poor exercise tolerance**, **muscle cramps**, and **rhabdomyolysis**. The prognosis is generally good and symptoms can be improved by consuming simple sugars before beginning physical activity.

During glycogenolysis, **glycogen phosphorylase** shortens glycogen chains by cleaving α-1,4-glycosidic linkages between glucose residues, liberating glucose 1-phosphate in the process. This occurs until 4 residues remain before a branch point (the "limit" dextrin). At this point, the debranching enzyme performs 2 enzymatic functions:

1. Glucosyltransferase cleaves the 3 outer glucose residues of the 4 that are left by glycogen phosphorylase and transfers them to a nearby branch
2. The enzyme α-1,6-glucosidase removes the single remaining branch residue, producing free glucose and a linear glycogen chain that can be further shortened by glycogen phosphorylase

(Choice B) The glucose 1-phosphate generated by glycogenolysis is converted by phosphoglucomutase to glucose-6-phosphate, which can then undergo glycolysis

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to glucose 6-phosphate, which can then undergo glycolysis.

(Choice C) Within the liver and kidney, glucose 6-phosphatase converts glucose 6-phosphate to glucose to help maintain blood glucose levels during periods of fasting. However, muscles lack glucose 6-phosphatase and so must utilize glucose 6-phosphate for glycolysis during muscle contraction.

(Choice D) The first step in the pentose phosphate pathway (hexose monophosphate pathway) is conversion of glucose 6-phosphate to 6-phosphogluconate by glucose-6-phosphate dehydrogenase. This pathway maintains cellular NADPH levels and produces pentose sugars for nucleotide synthesis.

(Choice E) Glucose 6-phosphate is converted into fructose 6-phosphate by glucose 6-phosphate isomerase during the second step of glycolysis.

Educational objective:
Glycogen serves as a source of glucose during fasting and as an energy store that can be mobilized quickly during strenuous muscle contraction. Myophosphorylase deficiency (McArdle disease or glycogen storage disease type V) causes failure of muscle glycogenolysis, resulting in decreased exercise tolerance, muscle pain and cramping, and myoglobinuria with physical activity.

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A 12-year-old boy is brought to the office due to gait instability and pruritic skin rash for the past several weeks. His mother reports that he has also been irritable and had loose stools during this time. The patient's childhood development has been unremarkable except for several episodes of similar skin rash that resolved spontaneously. Examination shows scaly, erythematous skin lesions in sun-exposed areas and cerebellar ataxia. Laboratory evaluation shows increased levels of neutral amino acids in the urine. This patient's symptoms would most likely respond to which of the following supplements?

A. Ascorbate
B. Folic acid
C. Niacin
D. Pyridoxine
E. Riboflavin
F. Thiamine
G. Tocopherol

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A. ~~Ascorbate~~ (2%)
B. ~~Folic acid~~ (2%)
C. Niacin (55%)
D. Pyridoxine (16%)
E. Riboflavin (4%)
F. Thiamine (11%)
G. Tocopherol (6%)

Correct
55%
01 min, 43 secs
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This patient likely has **Hartnup disease**, an autosomal recessive metabolic disorder caused by inactivating mutations affecting the **neutral amino acid transporter**. This results in impaired transport of neutral amino acids, particularly tryptophan, in the small intestine and proximal tubule of the kidney.

Tryptophan is an essential amino acid and a precursor for niacin, serotonin, and melatonin. Conversion of tryptophan to niacin is responsible for the generation of up to half of the nicotinamide adenine dinucleotide (NAD+) required for redox reactions; the clinical manifestations of Hartnup disease are primarily due to niacin deficiency. Patients present with intermittent attacks of **pellagra-like skin eruptions** (development of a red, rough rash following sun exposure) and **cerebellar ataxia** in early childhood that become less severe with increasing age.

The diagnosis is confirmed by detecting excessive amounts of neutral amino acids (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, and tryptophan) in the urine (**neutral aminoaciduria**). A high-protein diet along with daily niacin or nicotinamide supplementation generally results in significant symptom improvement.

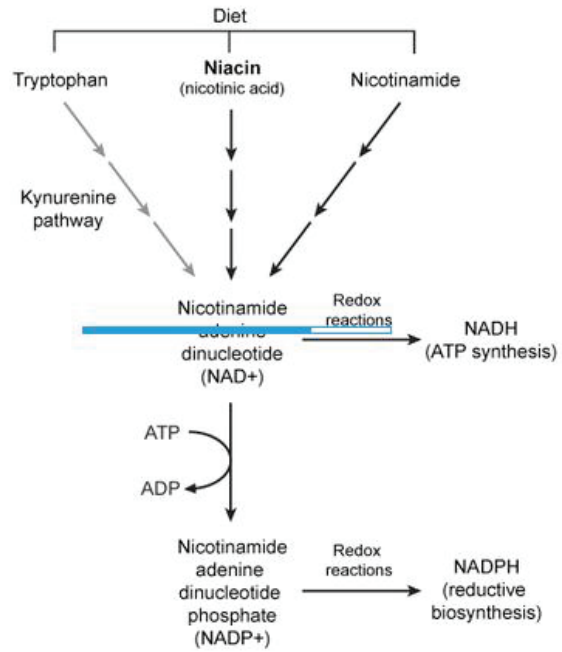
(Choice A) Ascorbate (vitamin C) is a water-soluble vitamin required for hydroxylation of proline and lysine residues during collagen synthesis. Deficiency results in scurvy, a disease characterized by bone pain, easy bruising, and poor wound healing.

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Niacin metabolism



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easy bruising, and poor wound healing.

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easy bruising, and poor wound healing.

(Choice B) Both folic acid and vitamin B_{12} deficiencies result in a megaloblastic anemia. However, neurologic manifestations of subacute combined degeneration of the posterior and lateral columns are specific to vitamin B_{12} deficiency.

(Choice D) Pyridoxine (vitamin B_6) acts as a coenzyme in the decarboxylation and transamination of amino acids, including the metabolism of tryptophan to niacin. Deficiency of pyridoxine leads to anemia, peripheral neuropathy, and dermatitis. Supplementation in Hartnup disease is not effective due to underlying tryptophan malabsorption.

(Choice E) The coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) form the prosthetic groups of several enzymes important in electron transport; both are synthesized from riboflavin (vitamin B_2). Clinical features of deficiency include sore throat, stomatitis, glossitis, normocytic anemia, and seborrheic dermatitis.

(Choice F) Thiamine use by the body is maximal in states of accelerated carbohydrate metabolism because thiamine acts as a cofactor for the enzymes transketolase (pentose phosphate pathway), α-ketoglutarate dehydrogenase (TCA cycle), and pyruvate dehydrogenase (forms acetyl-CoA).

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(Choice F) Thiamine use by the body is maximal in states of accelerated carbohydrate metabolism because thiamine acts as a cofactor for the enzymes transketolase (pentose phosphate pathway), α-ketoglutarate dehydrogenase (TCA cycle), and pyruvate dehydrogenase (forms acetyl-CoA).

(Choice G) Tocopherol (vitamin E) is a fat-soluble vitamin that functions as a scavenger of free radicals (antioxidant). Deficiency of vitamin E is rare but can result in neurologic dysfunction (ataxia, hyporeflexia, loss of sensation) as well as hemolytic anemia.

Educational objective:
Hartnup disease is caused by impaired transport of neutral amino acids in the small intestine and proximal tubule of the kidney. Symptoms include pellagra-like skin eruptions and cerebellar ataxia, which occur as a result of niacin deficiency. The diagnosis can be confirmed through detection of excessive amounts of neutral amino acids in the urine.

References

- Hartnup disease.

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A 34-year-old previously healthy man comes to the emergency department due to a 3-hour history of chest pain, diaphoresis, and dyspnea. He does not smoke, exercises regularly, and eats a balanced diet. His father died at age 56 from a myocardial infarction. His blood pressure is 110/70 mm Hg and pulse is 110/min and regular. Physical examination is unremarkable. ECG shows ST elevation in the anterolateral leads. Coronary angiogram reveals proximal left anterior descending artery stenosis and thrombosis, which is treated with angioplasty and stent placement. Laboratory results are as follows:

Total cholesterol	160 mg/dL	
Low-density lipoprotein	90 mg/dL	
Glucose, serum	98 mg/dL	
Homocysteine, plasma	21.5 µmol/L	(normal: 4-14 µmol/L)

Further testing reveals a homozygous mutation in the methylene tetrahydrofolate reductase gene that leads

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lipoprotein	90 mg/dL	
Glucose, serum	98 mg/dL	
Homocysteine, plasma	21.5 µmol/L	(normal: 4-14 µmol/L)

Further testing reveals a homozygous mutation in the methylene tetrahydrofolate reductase gene that leads to decreased enzymatic activity. Due to this defect, the patient most likely has impairment converting homocysteine to which of the following?

A. Cystathionine
B. Cysteine
C. Methionine
D. Methylmalonyl-CoA
E. Succinyl-CoA

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Glucose, serum	98 mg/dL	
Homocysteine, plasma	21.5 µmol/L	(normal: 4-14 µmol/L)

Further testing reveals a homozygous mutation in the methylene tetrahydrofolate reductase gene that leads to decreased enzymatic activity. Due to this defect, the patient most likely has impairment converting homocysteine to which of the following?

- A. Cystathionine (9%)
- B. Cysteine (10%)
- ✓ C. Methionine (68%)
- D. Methylmalonyl-CoA (9%)
- E. Succinyl-CoA (2%)

Correct

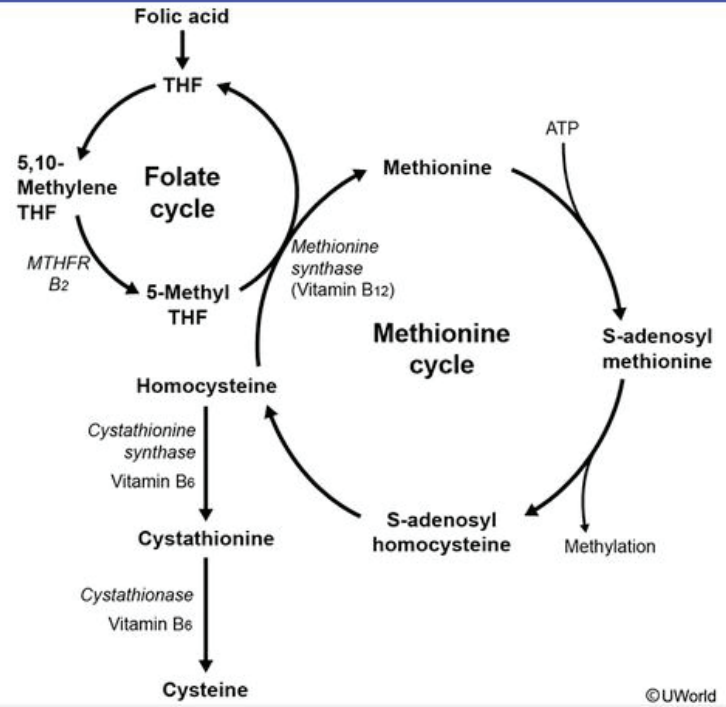
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Elevated levels of plasma homocysteine are an independent risk factor for **thrombotic events**, including venous thromboses, coronary artery disease, and ischemic stroke. The mechanism is thought to be due to direct and indirect induction of **endothelial damage**.

Homocysteine can be metabolized to **methionine** via remethylation or to **cystathionine** via transsulfuration. Remethylation to methionine occurs with the donation of a methyl group from methyl-tetrahydrofolate via **methionine synthase**, with vitamin B_{12} (cobalamin) as an important cofactor. Methyl-tetrahydrofolate is regenerated by the enzyme **methylene tetrahydrofolate reductase (MTHFR)**, using FAD as a cofactor. Homocysteine can also undergo transsulfuration via cystathionine-β-synthase to cystathionine **(Choice A)** and subsequently to cysteine **(Choice B)** via the enzyme cystathionase, using vitamin B_6 as a cofactor.

Elevations in plasma homocysteine can occur due to genetic mutations in critical enzymes and vitamin (cofactor) deficiencies. MTHFR deficiency is the most common genetic cause of hyperhomocysteinemia. Low levels of the B vitamins cobalamin, pyridoxine, and folate are associated with hyperhomocysteinemia. However, supplementation of B vitamins for patients with mildly to moderately elevated homocysteine levels has not demonstrated a decrease in cardiovascular risk or mortality.

(Choices D and E) Vitamin B_{12} is a cofactor for the enzyme methylmalonyl-CoA mutase in the conversion

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levels has not demonstrated a decrease in cardiovascular risk or mortality.

(Choices D and E) Vitamin B_{12} is a cofactor for the enzyme methylmalonyl-CoA mutase in the conversion of methylmalonyl-CoA to succinyl-CoA, a reaction that occurs in the breakdown of odd-chain fatty acids and some amino acids. As a result, patients with vitamin B_{12} deficiency have elevated methylmalonyl-CoA levels that subsequently result in buildup of neurotoxic methylmalonic acid. Symptomatic consequences include lethargy, seizures, paresthesias, and hypotonia. Homocysteine is elevated in both folate and vitamin B_{12} deficiencies, but methylmalonyl-CoA is elevated in vitamin B_{12} deficiency only.

Educational objective:

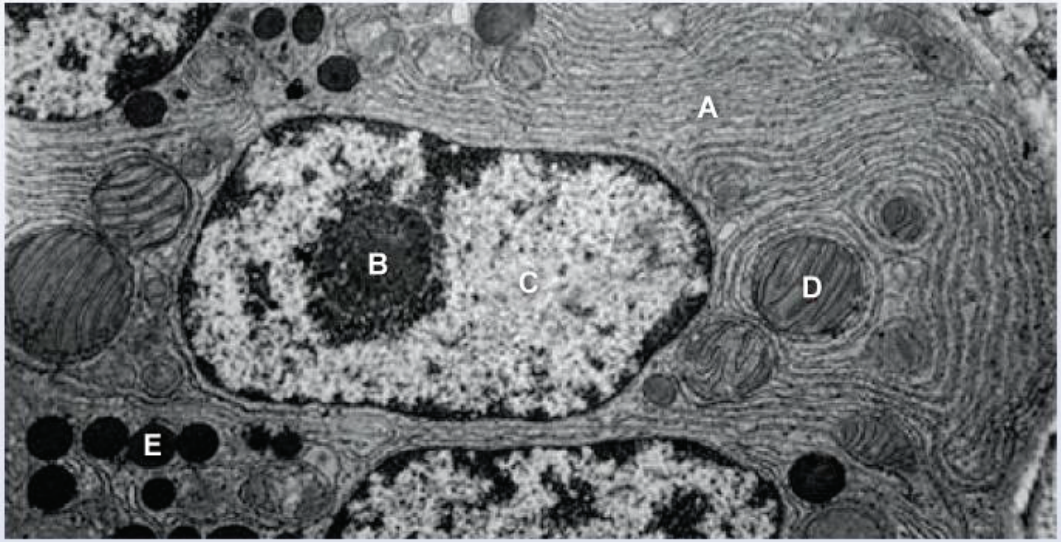
Elevated levels of plasma homocysteine are an independent risk factor for thrombotic events. Homocysteine can be metabolized to methionine via remethylation or to cystathionine via transsulfuration. Hyperhomocysteinemia is most commonly due to genetic mutations in critical enzymes or deficiencies of vitamin B_{12}, vitamin B_6, and folate.

References

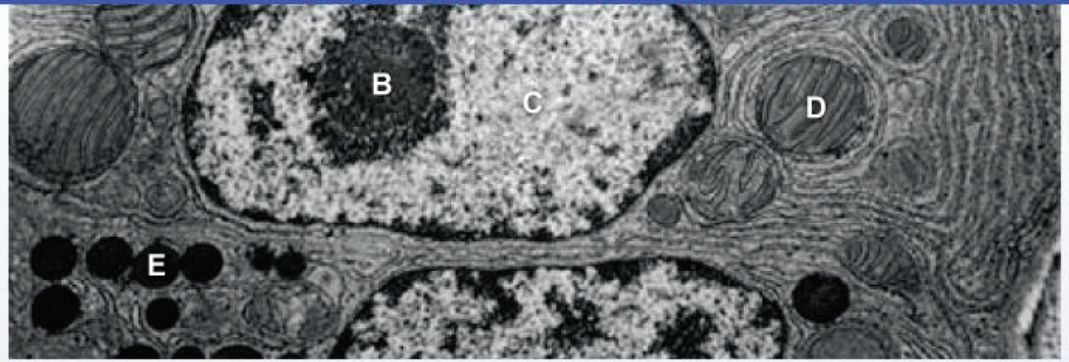
- Biochemistry of homocysteine in health and diseases.
- Homocysteine-lowering interventions for preventing cardiovascular events.

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Researchers analyzing eukaryotic genome structure and function perform an experiment to extract DNA from exocrine pancreatic cells. During the purification process, they isolate small circular DNA molecules that resemble a bacterial chromosome. Further analysis shows that these molecules code for proteins, transfer RNA, and ribosomal RNA. From which of the following cellular structures did these DNA molecules most likely originate?



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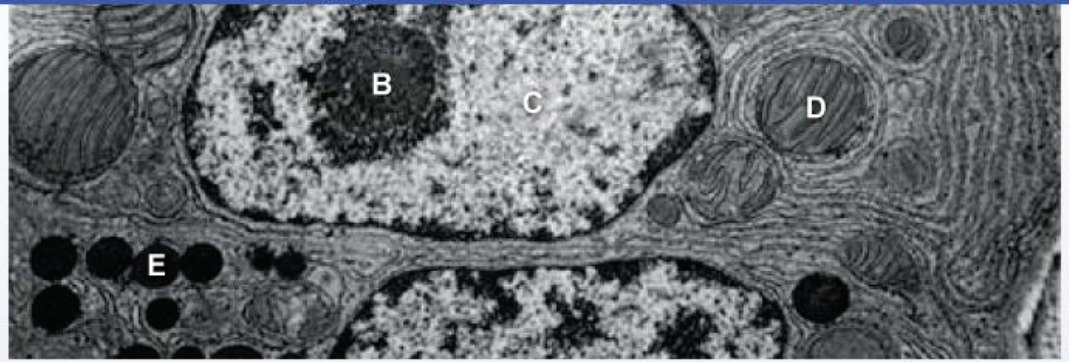


- A.A
- B.B
- C.C
- D.D
- E.E

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- A.A (4%)
- B.B (27%)
- C.C (12%)
- ✓ D.D (52%)
- E.E (3%)

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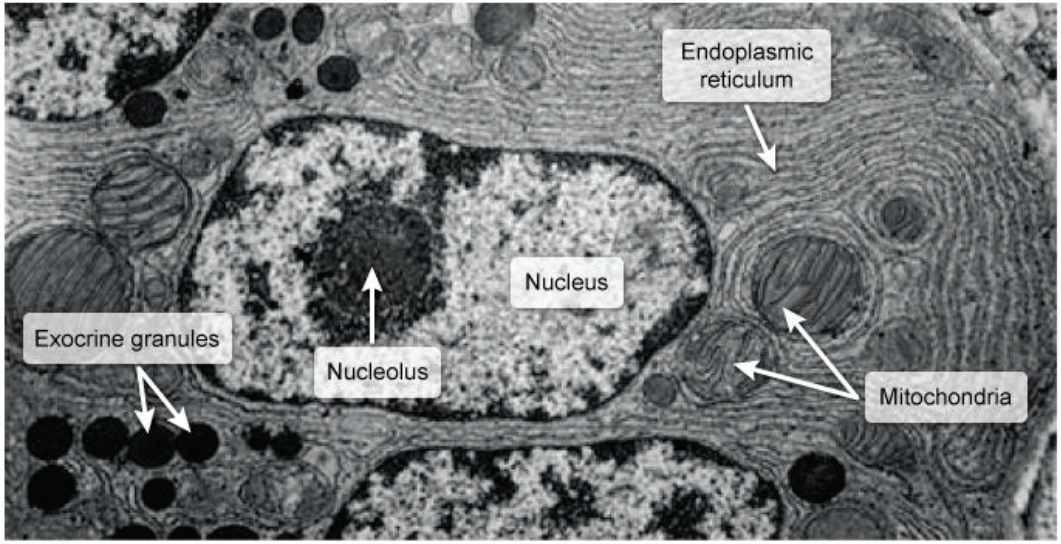
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Cellular organelles under electron microscopy



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Nuclear chromosomes contain most of the DNA found in human cells. However, mitochondria also contain their own DNA called **mitochondrial DNA** (mtDNA). This DNA exists as a **small circular chromosome** with a slightly different genetic code than that of nuclear DNA, consistent with the endosymbiotic theory that

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Nuclear chromosomes contain most of the DNA found in human cells. However, mitochondria also contain their own DNA called **mitochondrial DNA** (mtDNA). This DNA exists as a **small circular chromosome** with a slightly different genetic code than that of nuclear DNA, consistent with the endosymbiotic theory that mitochondria originated as prokaryotic cells that were later engulfed by ancient eukaryotes.

Over time, most of the genes coding for mitochondrial proteins have migrated to nuclear DNA. However, mtDNA still codes for about 14 proteins (some involved in oxidative metabolic pathways) and the ribosomal and transfer RNA needed for mitochondrial protein synthesis. Each mitochondrion contains 1-10 copies of **maternally derived** mtDNA. As a result, diseases arising from mutations in mtDNA are transmitted from the mother to all of her offspring.

Mitochondria can be identified on electron microscopy by their characteristic **double membrane and wavy cristae**.

(Choice A) The rough endoplasmic reticulum has a stippled appearance secondary to the presence of numerous ribosomes bound to its membranes. These ribosomes are involved in the synthesis of integral membrane proteins and proteins destined for export or packaging into granules or organelles.

(Choice B) The dark region identified within the nucleus is the nucleolus, the site of synthesis and assembly of eukaryotic ribosomal components. There is no lipid membrane separating the nucleolus from

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(Choice B) The dark region identified within the nucleus is the nucleolus, the site of synthesis and assembly of eukaryotic ribosomal components. There is no lipid membrane separating the nucleolus from the rest of the nucleus.

(Choice C) The lighter "electron-lucent" regions within the nucleus signify euchromatin (unpackaged DNA being actively transcribed).

(Choice E) This electron-dense membrane-bound spherical structure represents an exocrine granule containing enzymes and other proteins packaged for secretion.

Educational objective:
Mitochondrial DNA (mtDNA) is the most common non-nuclear DNA found in eukaryotic cells. It resembles prokaryotic DNA and is maternally derived. Mutations involving mtDNA (or nuclear DNA that codes for mitochondrial proteins) can cause a variety of mitochondrial disorders, including Leigh syndrome and MELAS.

Biochemistry	Biochemistry (General Principles)	Mitochondrial disorders
Subject	System	Topic

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A 35-year-old woman comes to the emergency department with nausea, vomiting, and fever. Her symptoms began 24 hours ago, and she has been unable to eat or drink anything since. She has a 3-year-old daughter who had similar symptoms 2 days earlier but is now fine. Laboratory studies show a blood glucose level of 82 mg/dL despite her 24-hour fast. Maintenance of this patient's blood glucose levels is facilitated by hepatic conversion of pyruvate into glucose. Which of the following substances directly stimulates the first enzyme involved in this process?

A. Acetyl-CoA
B. Alanine
C. Citrate
D. Fructose 2,6-bisphosphate
E. Lactate
F. Oxaloacetate

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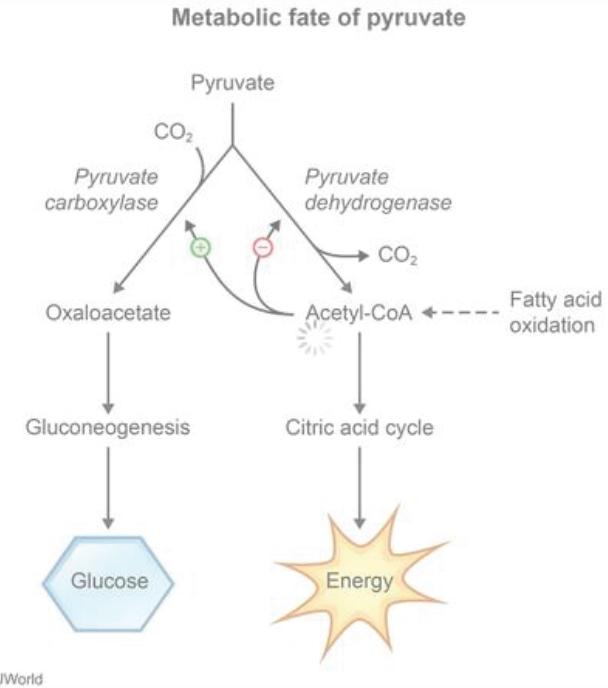
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- A. Acetyl-CoA (39%)
- B. Alanine (7%)
- C. Citrate (12%)
- D. Fructose 2,6-bisphosphate (17%)
- E. Lactate (6%)
- F. Oxaloacetate (16%)

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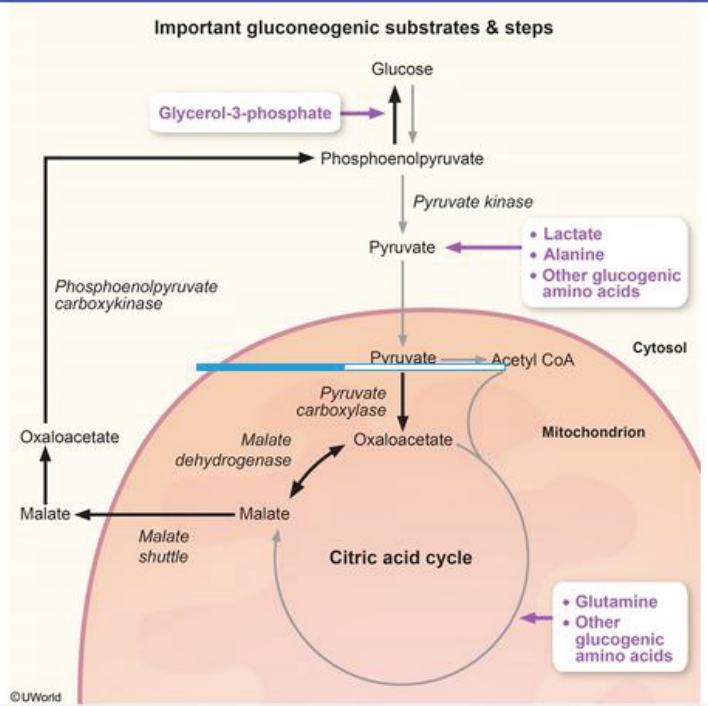
During gluconeogenesis, substances such as lactate and alanine are converted to pyruvate. However, pyruvate cannot be converted to phosphoenolpyruvate directly as pyruvate kinase is unidirectional. To convert pyruvate to phosphoenolpyruvate, pyruvate first undergoes biotin-dependent carboxylation to oxaloacetate in the mitochondria. This reaction is catalyzed by **pyruvate carboxylase**. The activity of pyruvate carboxylase is increased by **acetyl-CoA**. This critical regulatory step diverts pyruvate to pyruvate dehydrogenase when acetyl-CoA levels are too low, preventing the cell from becoming energy starved. When acetyl-CoA levels are high (as with increased beta oxidation of fatty acids during fasting), pyruvate carboxylase can operate at full capacity and convert most of the pyruvate into oxaloacetate for use in gluconeogenesis.

(Choice B) Muscle converts pyruvate to alanine via transamination, which is then transported to the liver where it is converted back to pyruvate for use in gluconeogenesis. Alanine allosterically inhibits pyruvate kinase, preventing phosphoenolpyruvate from being consumed by glycolysis during the gluconeogenic state.

(Choice C) Citrate is formed within mitochondria in the first reaction of the Krebs cycle, and elevated levels act as an indicator of high cellular energy stores and abundant biosynthetic intermediates. Citrate is

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state.

(Choice C) Citrate is formed within mitochondria in the first reaction of the Krebs cycle, and elevated levels act as an indicator of high cellular energy stores and abundant biosynthetic intermediates. Citrate is therefore an important positive regulator of acetyl-CoA carboxylase and fructose-1,6-bisphosphatase, key enzymes involved in fatty acid synthesis and gluconeogenesis, respectively.

(Choice D) Regulation of glycolysis and gluconeogenesis occurs mainly through the inverse regulation of phosphofructokinase-1 and fructose 1,6-bisphosphatase by fructose 2,6-bisphosphate. High levels of fructose 2,6-bisphosphate activate phosphofructokinase-1 and accelerate glycolysis; low levels disinhibit fructose 1,6-bisphosphatase and promote gluconeogenesis.

(Choice E) Lactate is an important source of carbon atoms for glucose synthesis during gluconeogenesis. During anaerobic glycolysis in skeletal muscle, pyruvate is reduced to lactate by lactate dehydrogenase. Lactate formed in the contracting muscles is released into the bloodstream and transported to the liver, where it is converted back into glucose.

(Choice F) Oxaloacetate is the product of pyruvate carboxylase during gluconeogenesis. As such, increased levels of oxaloacetate would decrease the activity of the enzyme.

Educational objective:

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phosphofructokinase-1 and fructose 1,6-bisphosphatase by fructose 2,6-bisphosphate. High levels of fructose 2,6-bisphosphate activate phosphofructokinase-1 and accelerate glycolysis; low levels disinhibit fructose 1,6-bisphosphatase and promote gluconeogenesis.

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(Choice F) Oxaloacetate is the product of pyruvate carboxylase during gluconeogenesis. As such, increased levels of oxaloacetate would decrease the activity of the enzyme.

Educational objective:

Acetyl-CoA stimulates gluconeogenesis by increasing the activity of pyruvate carboxylase when acetyl-CoA is abundant. This regulatory step allows pyruvate to be shunted toward acetyl-CoA production when acetyl-CoA levels are low, preventing the cell from becoming depleted of energy.

References

- Regulation of the structure and activity of pyruvate carboxylase by acetyl CoA.
- Allosteric regulation of the biotin-dependent enzyme pyruvate carboxylase by acetyl-CoA.

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The resting membrane potential for an isolated muscle cell is -70 mV. Equilibrium potentials for important ions are given below:

E_{Na} = + 60 mV
E_K = - 80 mV
E_{Cl} = - 70 mV
E_{Ca} = + 125 mV

Which of the following most likely forms the resting membrane potential of the cell?

A. High potassium conductance and some sodium conductance
B. High chloride conductance and some sodium conductance
C. High calcium conductance and some chloride conductance
D. High potassium conductance and some chloride conductance
E. High potassium conductance only

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ions are given below:

E_{Na} = + 60 mV
E_{K} = - 80 mV
E_{Cl} = - 70 mV
E_{Ca} = + 125 mV

Which of the following most likely forms the resting membrane potential of the cell?

- A. High potassium conductance and some sodium conductance (54%)
- B. ~~High chloride conductance and some sodium conductance~~ (4%)
- C. ~~High calcium conductance and some chloride conductance~~ (3%)
- D. ~~High potassium conductance and some chloride conductance~~ (14%)
- E. High potassium conductance only (22%)

Correct

54%

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The resting potential refers to the difference in charge across the cell membrane at rest (when there is no signaling activity). The membrane prevents the free diffusion of ions, and generally there is an excess of positive ions outside the cell and an excess of negative ions in the cytoplasm. This separation of positive and negative charges across the cell membrane gives rise to an electrical potential difference that ranges from -60 to -80 mV; the typical resting membrane potential of a cell is -70 mV.

The cytoplasm of a typical cell is characterized by a low concentration of Na and high concentration of K. The extracellular fluid is inversely rich in Na and low in K. This difference in Na and K concentration is maintained by the Na,K-ATPase, which pumps three Na ions out of the cell for every 2 K ions allowed into the cell.

Every charged ion that the cell membrane is permeable attempts to push the resting membrane potential of the cell toward its equilibrium potential. The resting membrane potential can therefore be viewed as a combination of the equilibrium potentials of the ions that can penetrate the cell membrane. Each permeable ion does not contribute equally to the membrane potential; it is obvious that the resting membrane potential does not equal the average of the different equilibrium potentials. The greater the permeability of a given ion, the greater its contribution to the resting membrane potential will be. Ions with little permeability will contribute very little to the resting membrane potential. In the resting cell the

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membrane potential does not equal the average of the different equilibrium potentials. The greater the permeability of a given ion, the greater its contribution to the resting membrane potential will be. Ions with little permeability will contribute very little to the resting membrane potential. In the resting cell the permeability of the membrane for K is much higher than that for Na. Outflow of K ions through non-gated channels maintains the negative charge inside the membrane, which approaches the equilibrium potential for K. There are, however, a small number of channels that allow the flow of Na into the cell. This small influx of Na ions decreases the membrane potential, and for this reason the resting potential of the membrane is always less negative than the equilibrium potential for K **(Choice A)**.

(Choice B) If the chloride equilibrium potential is -70 mV and the resting membrane potential is -70 mV, then chloride would need to be the only membrane permeable ion with no contribution from other ions. Chloride, in reality, plays little role in the determination of the membrane potential.

(Choice C) High calcium conductance would make the resting membrane potential positive, and the question stem states that the membrane potential is -70 mV.

(Choice D) High potassium conductance does occur at rest and is the largest contributor to the resting membrane potential. Chloride plays little to no role in the determination of the resting membrane potential.

(Choice E) If a high potassium conductance were the only contributor to the resting membrane potential,

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(Choice D) High potassium conductance does occur at rest and is the largest contributor to the resting membrane potential. Chloride plays little to no role in the determination of the resting membrane potential.

(Choice E) If a high potassium conductance were the only contributor to the resting membrane potential, then the membrane potential would be the same as the potassium equilibrium potential.

Educational Objective:
The resting membrane potential is the difference in the electrical charges across the cell membrane under steady-state conditions. The ions that are most permeable to the cell membrane make the largest contribution to the resting membrane potential. In general, a high potassium efflux and some sodium influx are responsible for the value of the resting potential, which is typically about -70 mV.

Biochemistry Biochemistry (General Principles) Resting membrane potential and action potential

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A pharmaceutical researcher is studying a target protein involved in the signal transduction and cellular response to TSH. The protein is isolated and purified from thyroid follicular cells. Further analysis reveals that the protein contains multiple alpha-helical regions. Each of these regions is composed of approximately 20 amino acid residues consisting primarily of valine, alanine, and isoleucine. This particular region of the protein most likely performs which of the following functions?

A. Anchoring to the cell membrane
B. Binding to an extracellular ligand
C. Binding to intranuclear DNA
D. Interacting with metal ions in transporting proteins
E. Phosphorylating tyrosine residues

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A pharmaceutical researcher is studying a target protein involved in the signal transduction and cellular response to TSH. The protein is isolated and purified from thyroid follicular cells. Further analysis reveals that the protein contains multiple alpha-helical regions. Each of these regions is composed of approximately 20 amino acid residues consisting primarily of valine, alanine, and isoleucine. This particular region of the protein most likely performs which of the following functions?

- A. Anchoring to the cell membrane (46%)
- B. Binding to an extracellular ligand (15%)
- C. Binding to intranuclear DNA (18%)
- D. Interacting with metal ions in transporting proteins (7%)
- E. Phosphorylating tyrosine residues (11%)

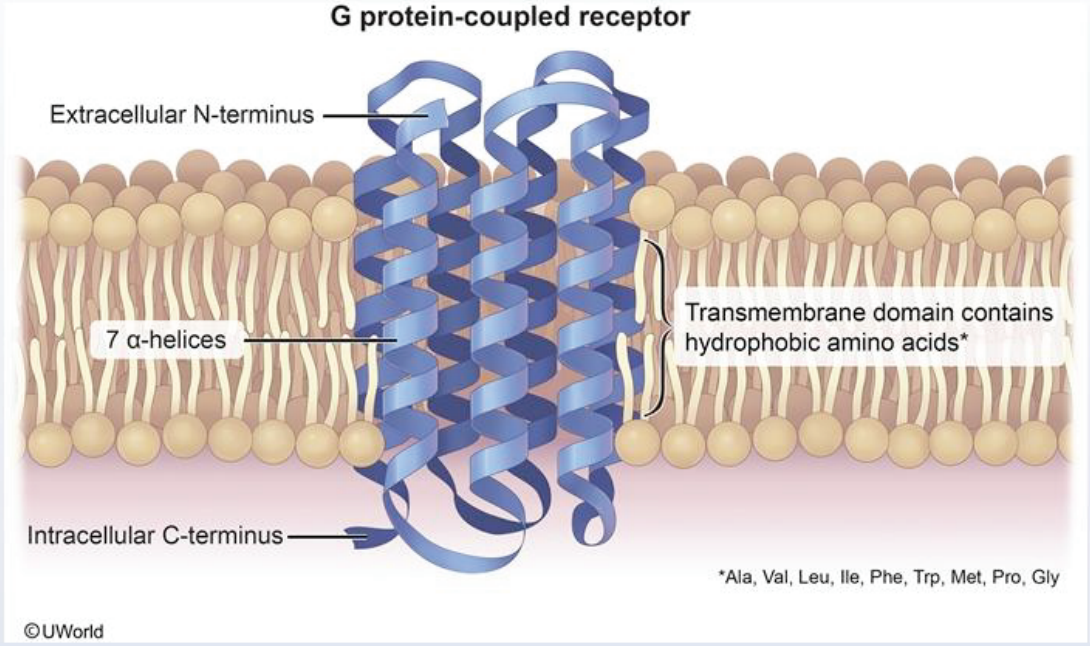
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G protein-coupled receptors that bind glycoprotein hormones (eg, TSH, LH, FSH) contain 3 major domains: an extracellular domain responsible for ligand binding, a transmembrane domain, and an intracellular domain coupled with heterotrimeric G proteins.

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intracellular domain coupled with heterotrimeric G proteins.

The **transmembrane domain** is made up of **nonpolar, hydrophobic amino acids** (eg, alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, proline, glycine). These amino acids are arranged in an alpha-helical fashion and project their hydrophobic R groups outwardly, **anchoring** the transmembrane region of the protein to the hydrophobic core of the **phospholipid bilayer**. The transmembrane domain may also play an important role in cellular signaling and transport.

(Choice B) Binding of a ligand to the extracellular domain of a transmembrane receptor can result in activation of the cAMP or phosphatidylinositol second messenger system, activation of receptor tyrosine kinases, opening of ion channels, and activation of the calcium-calmodulin system. The extracellular domain of these receptors is typically composed of hydrophilic amino acids.

(Choice C) Activation of G protein-coupled receptors utilizing the cAMP second messenger system results in increased synthesis of intracellular cAMP and subsequent activation of protein kinase A. Protein kinase A then phosphorylates cytosolic proteins that translocate into the nucleus and bind to DNA promoter regions to modulate transcription.

(Choice D) Intracellular iron-containing proteins (hemeproteins) include hemoglobin, myoglobin, and cytochrome oxidase. Heme is a complex of protoporphyrin IX and iron. Hemoglobin A, the most common

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(Choice D) Intracellular iron-containing proteins (hemeproteins) include hemoglobin, myoglobin, and cytochrome oxidase. Heme is a complex of protoporphyrin IX and iron. Hemoglobin A, the most common hemoglobin in adults, consists of 2 alpha and 2 beta globin chains held together by noncovalent interactions. Each subunit contains stretches of alpha helices that form a heme-binding pocket lined by nonpolar amino acids.

(Choice E) Insulin and IGF-1 bind to receptors that possess tyrosine kinase on their intracellular domain (receptor tyrosine kinases). These receptors dimerize upon ligand binding to the extracellular domain, which subsequently activates tyrosine kinase. Tyrosine kinase phosphorylates tyrosine residues, triggering a downstream cellular response.

Educational objective:
Integral membrane proteins contain transmembrane domains composed of alpha helices with hydrophobic amino acid residues (eg, alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, proline, glycine). These transmembrane domains help anchor the protein to the phospholipid bilayer of the cell membrane.

References

- G protein coupled receptor structure and activation

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A 6-month-old girl is brought to the office by her mother for a checkup appointment. The mother states, "My baby doesn't seem to be growing much despite feeding as often as my previous children. I am worried that something is wrong with her." Physical examination shows hepatomegaly, hypotonia, and height and weight below the 10th percentile. Laboratory studies show hypoglycemia and ketoacidosis. A liver biopsy shows hepatic fibrosis without fat accumulation. Further analysis reveals abundant quantities of a multibranched polysaccharide with abnormally short outer chains within the cytosol of the hepatocytes. Which of the following enzymes is most likely deficient in this patient?

A. Acid maltase
B. Debranching enzyme
C. Glucose-6-phosphatase
D. Liver glycogen phosphorylase
E. Muscle glycogen phosphorylase
F. Pyruvate kinase

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"My baby doesn't seem to be growing much despite feeding as often as my previous children. I am worried that something is wrong with her." Physical examination shows hepatomegaly, hypotonia, and height and weight below the 10th percentile. Laboratory studies show hypoglycemia and ketoacidosis. A liver biopsy shows hepatic fibrosis without fat accumulation. Further analysis reveals abundant quantities of a multibranched polysaccharide with abnormally short outer chains within the cytosol of the hepatocytes. Which of the following enzymes is most likely deficient in this patient?

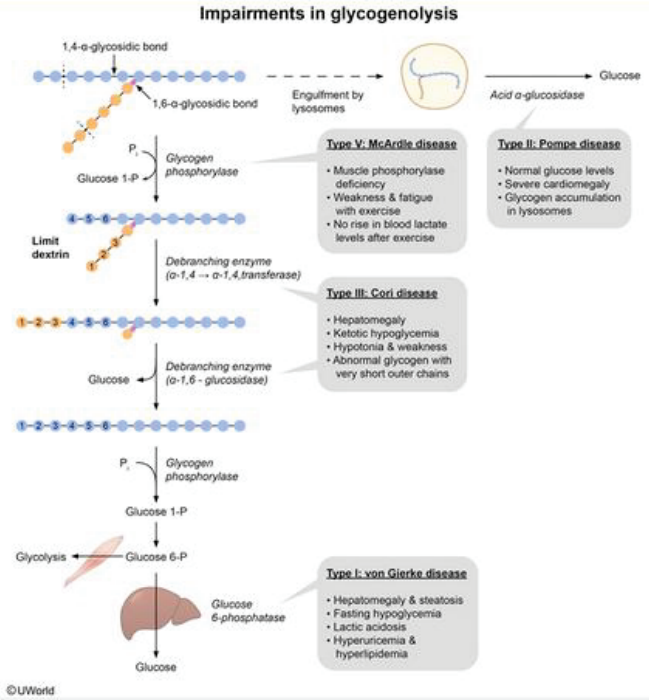
A. Acid maltase (2%)
B. Debranching enzyme (69%)
C. Glucose-6-phosphatase (13%)
D. Liver glycogen phosphorylase (10%)
E. Muscle glycogen phosphorylase (1%)
F. Pyruvate kinase (1%)

Correct
69%
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01/10/2021

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Debranching enzyme deficiency (Cori disease) usually presents in infancy or childhood with both liver and muscle involvement. Symptoms include **hypoglycemia**, **hepatomegaly**, and ketoacidosis. Muscle weakness and **hypotonia** help to distinguish the condition from other glycogen storage diseases with hepatic involvement (eg, von Gierke, Hers). Hepatic fibrosis is common, but fatty infiltration is not usually seen. A key distinguishing feature is cytosolic accumulation of glycogen with abnormally **short outer chains** (limit dextrins).

During glycogenolysis, glycogen phosphorylase shortens glycogen chains by cleaving α-1,4-glycosidic linkages between glucose residues, liberating glucose-1-phosphate in the process. This occurs until 4 residues remain before a branch point (the limit dextrin). At this point, **debranching enzyme** performs 2 enzymatic functions:

1. Glucosyltransferase cleaves the outer 3 residues of the 4 glucose residues left by glycogen phosphorylase and transfers them to a nearby branch
2. α-1,6-glucosidase removes the single remaining branch residue, producing free glucose and a linear glycogen chain that can be further shortened by glycogen phosphorylase

(Choice A) Small amounts of glycogen are broken down by the lysosomal enzyme acid maltase (has both α-1,4- and α-1,6-glucosidase activity). Acid maltase deficiency (Pompe disease) is characterized by cardiomegaly, severe generalized hypotonia, and lysosomal glycogen accumulation (hypoglycemia is not

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(Choice A) Small amounts of glycogen are broken down by the lysosomal enzyme acid maltase (has both α-1,4- and α-1,6-glucosidase activity). Acid maltase deficiency (Pompe disease) is characterized by cardiomegaly, severe generalized hypotonia, and lysosomal glycogen accumulation (hypoglycemia is not seen).

(Choice C) Glucose-6-phosphatase deficiency (von Gierke disease) affects mainly the liver and kidney, as the enzyme is not expressed in significant quantities in muscle tissue. Major symptoms include hypoglycemia, lactic acidosis, hyperlipidemia, and hyperuricemia. Hepatic steatosis is a cardinal manifestation of the disorder.

(Choice D) Liver glycogen phosphorylase deficiency (Hers disease) presents in early childhood with mild hypoglycemia, ketosis, and hepatomegaly. However, it does not affect skeletal muscles and would show an excess of normally structured glycogen (not limit dextrins) on liver biopsy.

(Choice E) Muscle glycogen phosphorylase deficiency causes McArdle disease, a condition that presents with decreased exercise tolerance, muscle pain and cramping during strenuous activity, and myoglobinuria. Blood lactate is often very low after exercise, and muscle biopsy shows an excess of normally structured glycogen.

(Choice F) Pyruvate kinase converts phosphoenolpyruvate to pyruvate during glycolysis. Pyruvate kinase

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hypoglycemia, ketosis, and hepatomegaly. However, it does not affect skeletal muscles and would show an excess of normally structured glycogen (not limit dextrins) on liver biopsy.

(Choice E) Muscle glycogen phosphorylase deficiency causes McArdle disease, a condition that presents with decreased exercise tolerance, muscle pain and cramping during strenuous activity, and myoglobinuria. Blood lactate is often very low after exercise, and muscle biopsy shows an excess of normally structured glycogen.

(Choice F) Pyruvate kinase converts phosphoenolpyruvate to pyruvate during glycolysis. Pyruvate kinase deficiency causes chronic hemolytic anemia as glycolysis is the main source of energy for erythrocytes.

Educational objective:
Debranching enzyme deficiency (Cori disease) leads to accumulation of glycogen with abnormally short outer chains (limit dextrins) due to the inability to degrade α-1,6-glycosidic branch points. Patients present with hypoglycemia, ketoacidosis, hepatomegaly, and muscle weakness and hypotonia.

Biochemistry	Biochemistry (General Principles)	Glycogen storage disease
Subject	System	Topic

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An 8-month-old boy is evaluated for developmental delay, failure to thrive, and episodic seizures. Physical examination shows ophthalmoplegia and hypotonia. Laboratory studies reveal an elevated serum lactate level. Further histochemical studies show severely reduced pyruvate dehydrogenase enzyme activity in both freshly isolated peripheral blood lymphocytes and cultured fibroblasts. Increasing which of the following substances in his diet is most likely to help this patient generate energy without further elevating lactate levels?

- A. Alanine
- B. Asparagine
- C. Galactose
- D. Glycerol
- E. Lysine
- F. Serine

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An 8-month-old boy is evaluated for developmental delay, failure to thrive, and episodic seizures. Physical examination shows ophthalmoplegia and hypotonia. Laboratory studies reveal an elevated serum lactate level. Further histochemical studies show severely reduced pyruvate dehydrogenase enzyme activity in both freshly isolated peripheral blood lymphocytes and cultured fibroblasts. Increasing which of the following substances in his diet is most likely to help this patient generate energy without further elevating lactate levels?

A. Alanine (32%)
B. Asparagine (10%)
C. Galactose (7%)
D. Glycerol (14%)
E. Lysine (32%)
F. Serine (2%)

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This patient has **pyruvate dehydrogenase deficiency**, an inherited inborn error of metabolism often presenting in infancy with lactic acidosis and neurologic defects. The disease results from deficient activity of the pyruvate dehydrogenase complex, a multi-enzyme complex generating acetyl-CoA from pyruvate, thereby linking glycolysis and the TCA cycle. Dietary carbohydrates are broken down into pyruvate via glycolysis; in patients with pyruvate dehydrogenase deficiency, the lack of enzymatic activity leads to a **buildup of pyruvate**, which is shunted to lactate via lactate dehydrogenase, generating a potentially life-threatening **lactic acidosis**.

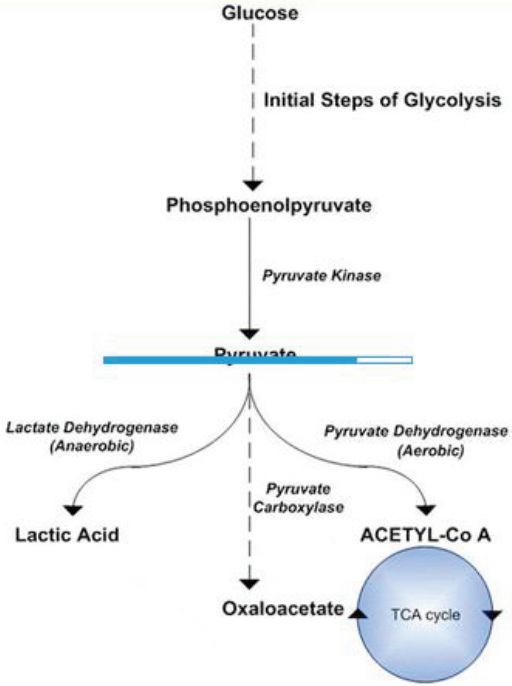
Disease management involves the implementation of a **ketogenic diet**: a high-fat, low-carbohydrate diet with moderate levels of protein. This diet forces the production of ketone bodies from fat and amino acid catabolism to fuel the body in the place of glucose. The near-absence of glucose in the diet decreases the amount of pyruvate generated, thereby decreasing lactate levels.

Amino acid catabolism results in formation of intermediates that are referred to as glucogenic, ketogenic, or both. Glucogenic amino acid metabolism produces pyruvate or TCA cycle intermediates, which can be converted to glucose via gluconeogenesis. Ketogenic amino acid metabolism generates the ketone body precursor acetyl-CoA. **Lysine** and **leucine** are **exclusively ketogenic** amino acids; they cannot be

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metabolized to pyruvate and consumption will not lead to increased production of lactic acid.

(Choices A and F) The non-essential glucogenic amino acids alanine and serine can be converted to pyruvate through a transamination reaction catalyzed by alanine transaminase and a deamination reaction catalyzed by serine dehydratase, respectively.

(Choice B) Asparagine is catabolized to aspartate and subsequently transaminated to produce glutamate and oxaloacetate, an intermediate of the TCA cycle. Oxaloacetate by itself cannot be used to produce energy; it must first undergo condensation with acetyl-CoA to form citrate.

(Choice C) The monosaccharide galactose is metabolized in the glycolytic pathway; dietary intake will result in elevated levels of lactate in patients with pyruvate dehydrogenase deficiency.

(Choice D) Glycerol is metabolized to glyceraldehyde 3-phosphate, a glycolysis intermediate. It can be used as a substrate to form pyruvate and, subsequently, lactate.

Educational objective:
Pyruvate dehydrogenase complex deficiency is an inherited inborn error of metabolism causing lactic acidosis and neurologic defects. Patients are unable to convert pyruvate to acetyl-CoA, resulting in a shunting of pyruvate to lactic acid. In these patients, metabolism of exclusively ketogenic amino acids (eg,

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(Choice D) Glycerol is metabolized to glyceraldehyde 3-phosphate, a glycolysis intermediate. It can be used as a substrate to form pyruvate and, subsequently, lactate.

Educational objective:
Pyruvate dehydrogenase complex deficiency is an inherited inborn error of metabolism causing lactic acidosis and neurologic defects. Patients are unable to convert pyruvate to acetyl-CoA, resulting in a shunting of pyruvate to lactic acid. In these patients, metabolism of exclusively ketogenic amino acids (eg, lysine, leucine) can provide energy in the form of acetyl-CoA without increasing lactate production.

References

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A 42-year-old woman comes to the neurologist for enrollment in a research study. She has a 15-year history of resting tremor, bradykinesia, and cogwheel rigidity consistent with Parkinson's disease. One of her siblings recently started having similar symptoms. Genetic analysis is performed on the patient and her affected sibling. The results show a loss-of-function mutation in a gene that leads to an accumulation of misfolded proteins. Which of the following biochemical processes is most likely defective in this patient?

A. Acetylation
B. Gamma-carboxylation
C. Glucuronidation
D. Phosphorylation
E. Ubiquitination

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A 42-year-old woman comes to the neurologist for enrollment in a research study. She has a 15-year history of resting tremor, bradykinesia, and cogwheel rigidity consistent with Parkinson's disease. One of her siblings recently started having similar symptoms. Genetic analysis is performed on the patient and her affected sibling. The results show a loss-of-function mutation in a gene that leads to an accumulation of misfolded proteins. Which of the following biochemical processes is most likely defective in this patient?

- A. Acetylation (7%)
- B. ~~Gamma-carboxylation~~ (5%)
- C. ~~Glucuronidation~~ (2%)
- D. ~~Phosphorylation~~ (6%)
- ✓ E. Ubiquitination (78%)

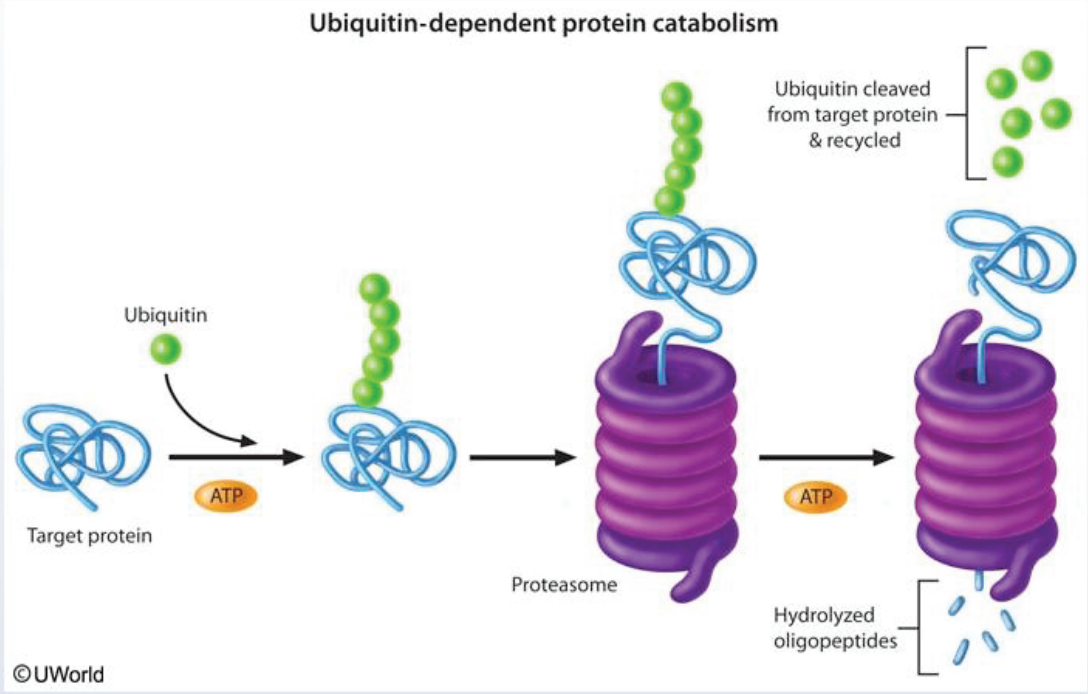
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Ubiquitin is a protein found in all eukaryotic cells that undergoes ATP-dependent attachment to other proteins, labeling them for degradation. The proteasome then recognizes these ubiquinated proteins and

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Ubiquitin is a protein found in all eukaryotic cells that undergoes ATP-dependent attachment to other proteins, labeling them for degradation. The proteasome then recognizes these ubiquinated proteins and uses ATP energy to drive them through its tubular structure, degrading them into small peptides in the process. Attachment of 4 or more ubiquitin monomers is required before most proteins are allowed entry into the proteasome. Ubiquitination plays an important role in many cell functions, including antigen processing, muscle wasting, cell cycle regulation, DNA repair, and disposal of misfolded proteins and regulatory enzymes.

Impairment of the ubiquitin-proteasome system can contribute to the development of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. Failure of the system to properly degrade abnormal proteins causes protein misfolding, aggregation, and eventual obstruction of intracellular molecular traffic, leading to cell death. Together, the Parkin, PINK1, and DJ-1 genes code for a protein complex that promotes the degradation of misfolded proteins via the ubiquitin-proteasome system. Mutations in Parkin, PINK1, and DJ-1 are each associated with autosomal recessive forms of Parkinson's disease that have an early age of onset (< 50 years).

(Choice A) Heterochromatin is condensed and methylated DNA that has a low level of transcriptional activity. In contrast to heterochromatin, euchromatin (loosely arranged chromatin) has very high levels of

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disease that have an early age of onset (< 50 years).

(Choice A) Heterochromatin is condensed and methylated DNA that has a low level of transcriptional activity. In contrast to heterochromatin, euchromatin (loosely arranged chromatin) has very high levels of transcriptional activity. Histone acetylation promotes the formation of euchromatin.

(Choice B) Vitamin K-dependent gamma-carboxylation is critical for the functioning of clotting factors II, VII, IX, and X, and of the anticoagulative proteins C and S. Warfarin inhibits carboxylation of these proteins.

(Choice C) The hepatic processing of bilirubin is accomplished in three key steps: carrier-mediated passive uptake of bilirubin at the sinusoidal membrane; conjugation of bilirubin with glucuronic acid in the endoplasmic reticulum; and active biliary excretion of the water-soluble, nontoxic bilirubin-glucuronides. Disruption of this process occurs in Crigler-Najjar syndrome, a condition in which patients lack the enzyme needed to catalyze bilirubin glucuronidation.

(Choice D) Phosphorylation is the addition of a phosphate group (PO_4^{3-}) to a protein or other organic molecule. Phosphorylation is commonly involved in the regulation of enzymatic activity.

Educational objective:

Ubiquitin is a protein that undergoes ATP-dependent attachment to other proteins, labeling them for

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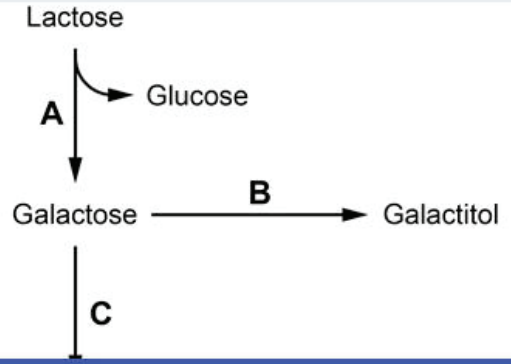
(Choice D) Phosphorylation is the addition of a phosphate group (PO_4^{3-}) to a protein or other organic molecule. Phosphorylation is commonly involved in the regulation of enzymatic activity.

Educational objective:
Ubiquitin is a protein that undergoes ATP-dependent attachment to other proteins, labeling them for degradation. These modified proteins enter the proteasome and are degraded into small peptides. Impairment of the ubiquitin-proteasome system can contribute to the development of neurodegenerative disorders, including Parkinson's and Alzheimer's diseases.

References

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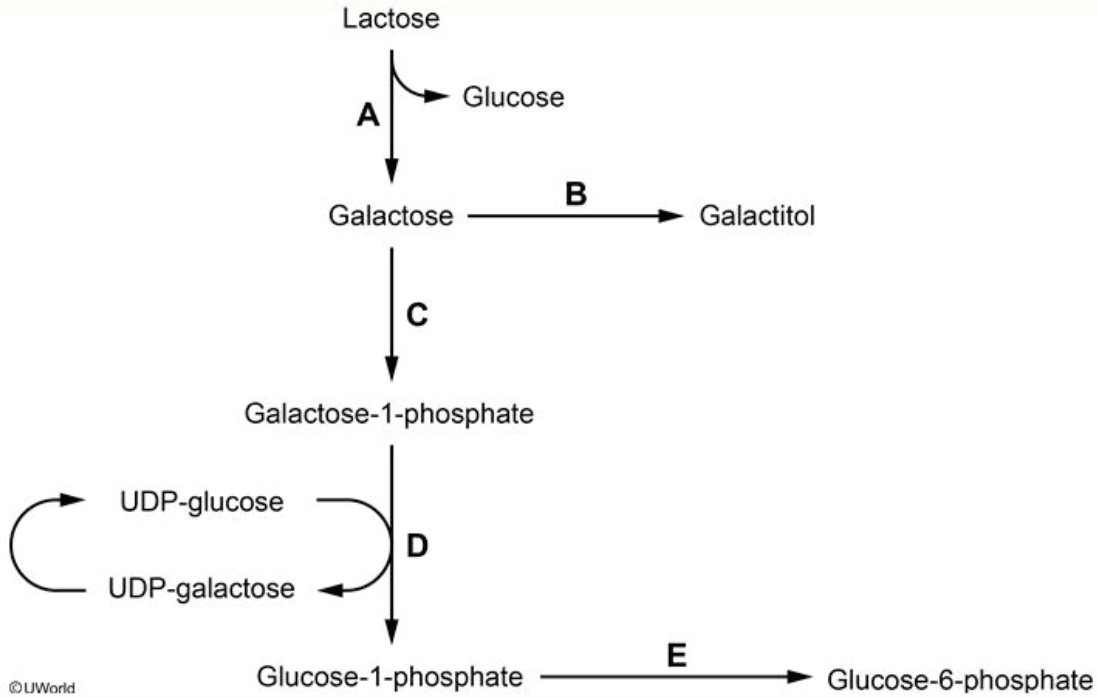
A 5-day-old term newborn is brought to the emergency department for multiple episodes of emesis. The breastfed infant has been having fewer wet diapers over the last 2 days. Vital signs show tachycardia, tachypnea, and hypotension. Physical examination shows an icteric, lethargic baby with a sunken fontanelle, dry mucous membranes, and hepatomegaly. A blood culture is drawn and empiric antibiotics are initiated. Hematologic studies show leukocytosis with bandemia. Serum studies show hypoglycemia and elevated transaminases. The ammonia level is normal. Newborn screen is pending. Preliminary results from arterial blood culture show gram-negative rods. The infant is placed on a special formula and gradually improves over the next few days. Which of the following steps in metabolism is most likely impaired in this patient?



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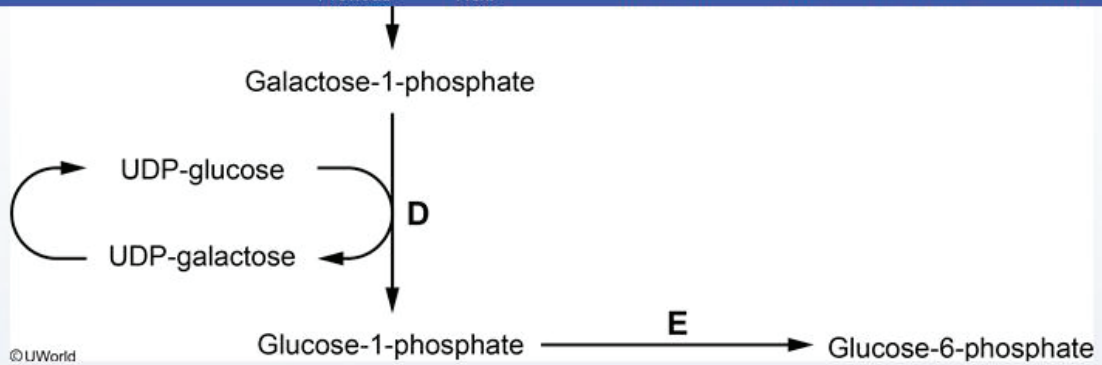
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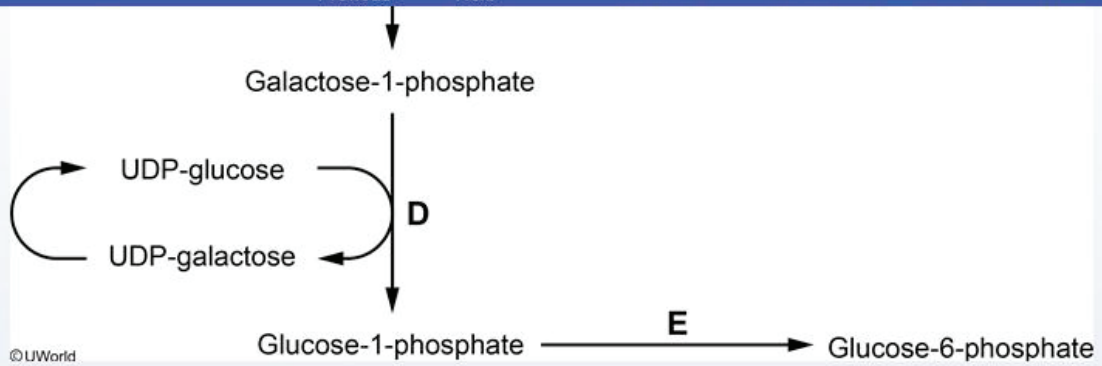
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- A.A
- B.B
- C.C
- D.D
- E.E

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- A.A (16%)
- B.B (3%)
- C.C (11%)
- D.D (58%)
- E.E (10%)

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Clinically relevant disorders of galactose metabolism	
Enzyme	**Clinical features**
Galactose-1-phosphate uridyl transferase	Jaundice, vomiting, hepatomegaly, renal dysfunction (aminoaciduria, hyperchloremic metabolic acidosis) *Escherichia coli* sepsis, cataract, hemolytic anemia
Galactokinase	Cataracts, rarely pseudotumor cerebri (galactitol accumulation)

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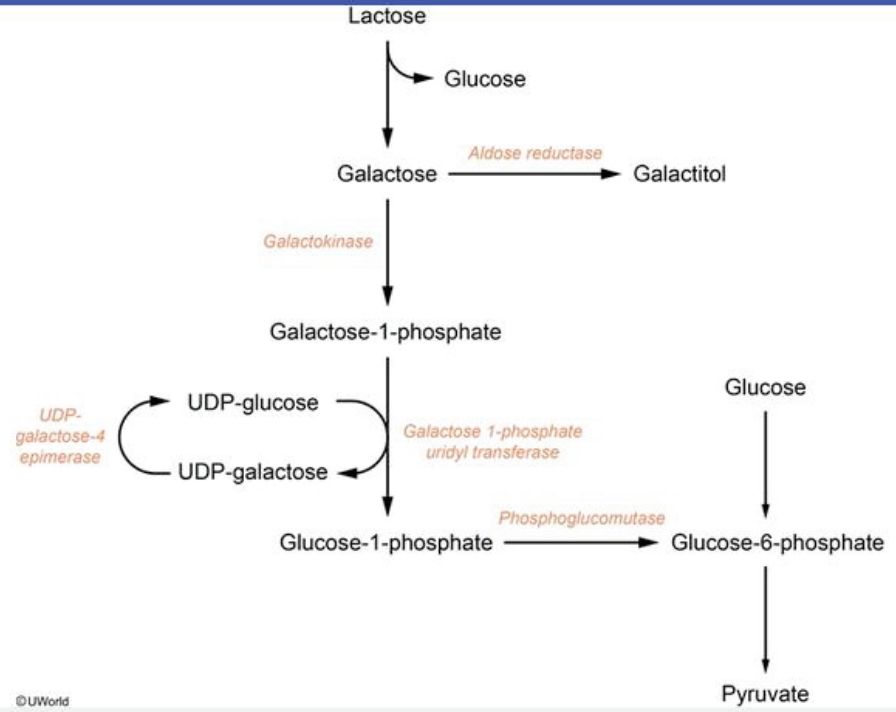
Lactose (milk sugar) is degraded by lactase, the intestinal disaccharidase, to galactose and glucose. Galactose is then phosphorylated to galactose-1-phosphate by the enzyme galactokinase (GALK). Galactose-1-phosphate is converted to glucose-1-phosphate by epimerization with transfer of uridine diphosphate (UDP) from UDP-glucose to UDP-galactose. This reaction is catalyzed by **galactose-1-phosphate uridyl transferase (GALT)**. UDP-galactose is then epimerized to UDP-glucose by UDP-galactose-4 epimerase. Although GALT deficiency is the most common form, a defect in any of these three enzymes can cause galactosemia.

Galactosemia can present with **vomiting** and lethargy soon after initiation of **breastfeeding**. In GALT

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Galactosemia can present with vomiting and lethargy soon after initiation of breastfeeding. In GALT

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Galactosemia can present with **vomiting** and lethargy soon after initiation of **breastfeeding**. In GALT deficiency, toxicity of accumulated galactose-1-phosphate is responsible for impaired liver function (transaminitis, hyperbilirubinemia, hypoglycemia) and renal dysfunction (hyperchloremic metabolic acidosis, aminoaciduria). Patients are also predisposed to *Escherichia coli* (gram-negative rod) **sepsis**.

Restricting lactose intake (eg, breast milk) and initiation of soy milk-based formula can result in regression of cataracts and improvement in renal and liver function. Soy milk consists of sucrose, which is metabolized to glucose and fructose. Glucose and fructose do not need GALT or GALK to enter the glycolytic pathway and generate energy.

(Choice A) Lactase hydrolyzes lactose to galactose in the small intestine. Primary lactase deficiency causes lactose intolerance and is rare in neonates.

(Choice B) Aldose reductase converts galactose to galactitol. GALT and GALK deficiency can lead to galactitol accumulation in the lens, which can lead to **cataract** formation in patients with galactosemia. However, aldose reductase deficiency does not cause galactosemia.

(Choice C) GALK phosphorylates galactose and its deficiency typically causes less severe manifestations of galactosemia with cataract formation (due to galactitol) being the most common manifestation. Because galactose-1-phosphate does not accumulate, liver and renal functions are preserved.

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galactitol accumulation in the lens, which can lead to **cataract** formation in patients with galactosemia. However, aldose reductase deficiency does not cause galactosemia.

(Choice C) GALK phosphorylates galactose and its deficiency typically causes less severe manifestations of galactosemia with cataract formation (due to galactitol) being the most common manifestation. Because galactose-1-phosphate does not accumulate, liver and renal functions are preserved.

(Choice E) Phosphoglucomutase isomerizes glucose-1-phosphate to glucose-6-phosphate, which then enters the glycolytic pathway. Its deficiency is rare. In GALT deficiency, accumulation of galactose-1-phosphate blocks phosphoglucomutase, thereby preventing energy production via glycolysis.

Educational objective:

Classic galactosemia results from deficiency of galactose-1-phosphate uridyl transferase. Clinical features include vomiting, lethargy, jaundice, and *Escherichia coli* sepsis. Cessation of breastfeeding and switching to soy milk-based formula is recommended.

References

- Galactosemia: when is it a newborn screening emergency?

Biochemistry | Biochemistry (General Principles) | Galactosemia

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A 4-day-old boy born to a 23-year-old woman is brought to the office for evaluation of poor feeding and vomiting. The pregnancy was uneventful and the mother had a normal delivery. Family history is noncontributory. The patient's temperature is 37.2 C (99 F), blood pressure is 60/30 mm Hg, pulse is 110/min, and respirations are 56/min. Physical examination reveals a lethargic newborn with exaggerated deep tendon reflexes and clonus. Further investigation reveals that the patient has an inherited condition that results in impaired transport of ornithine from the cytosol to the mitochondria. Nutritional restriction of which of the following substances can improve this patient's condition?

A. Branched-chain amino acids
B. Fructose
C. Galactose
D. Medium-chain triglycerides
E. Phenylalanine
F. Proteins
G. Pyridoxine

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noncontributory. The patient's temperature is 37.2 C (99 F), blood pressure is 60/50 mm Hg, pulse is 110/min, and respirations are 56/min. Physical examination reveals a lethargic newborn with exaggerated deep tendon reflexes and clonus. Further investigation reveals that the patient has an inherited condition that results in impaired transport of ornithine from the cytosol to the mitochondria. Nutritional restriction of which of the following substances can improve this patient's condition?

A. Branched-chain amino acids (18%)
B. Fructose (2%)
C. Galactose (2%)
D. Medium-chain triglycerides (14%)
E. Phenylalanine (7%)
✓ F. Proteins (52%)
G. Pyridoxine (3%)

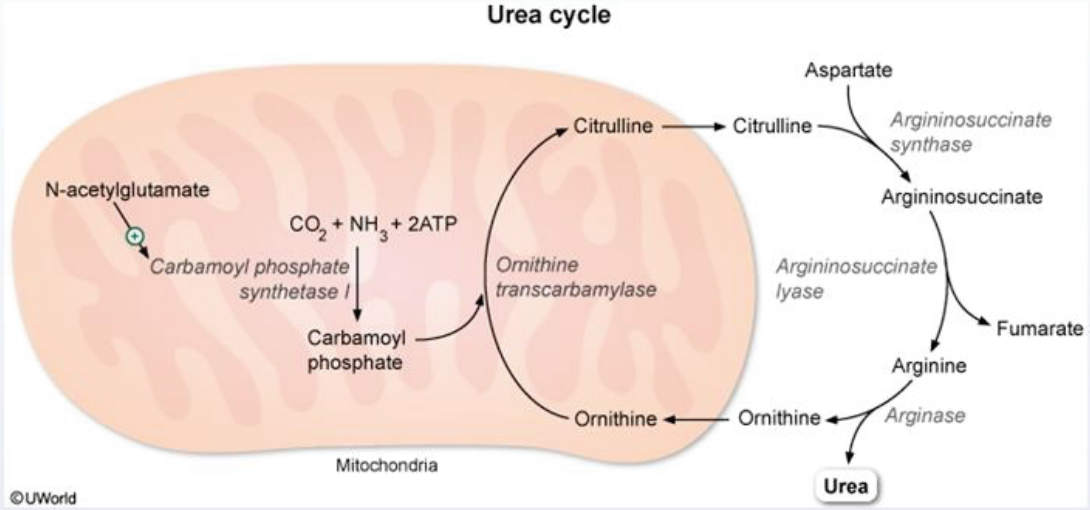
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Impaired transport of ornithine into the mitochondria can be caused by ornithine translocase deficiency, which results in a defect in the **hepatic urea cycle**. The urea cycle converts ammonia, which is generated from the **catabolism of amino acids**, into urea for excretion in urine. Urea cycle **defects** cause **ammonia to accumulate** in the blood, resulting in progressive lethargy, vomiting, seizures, and cerebral edema (may cause hyperreflexia and abnormal posturing when severe) in infancy and early childhood; milder defects caused by partial enzyme deficiencies may not manifest until adulthood.

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caused by partial enzyme deficiencies may not manifest until adulthood.

Effective treatment of urea cycle disorders requires balancing dietary protein intake and metabolic requirements. **Protein restriction** is the main treatment for urea cycle disorders, such that the body receives the essential amino acids needed for growth and development but not in excess such that excessive ammonia is formed. Medications that provide an alternate pathway to excrete nitrogen (eg, phenylacetate) are also used to help remove ammonia from the blood.

(Choice A) Restriction of branched-chain amino acids (eg, valine, leucine, isoleucine) is used to treat maple syrup urine disease (branched-chain alpha-ketoacid dehydrogenase deficiency) and propionic acidemia (propionyl-CoA carboxylase).

(Choice B) Fructose and sucrose restriction is the treatment for fructose 1-phosphate aldolase (aldolase B) deficiency. This condition causes vomiting and hypoglycemia in infants after fruit or juice is introduced.

(Choice C) Galactose and lactose are excluded from the diet in patients with classic galactosemia (absent galactose-1-phosphate uridyltransferase). Galactosemia presents in neonates with jaundice, vomiting, poor feeding, lethargy, hypoglycemia, and galactose-1-phosphate accumulation.

(Choice D) Medium-chain triglycerides are restricted in medium-chain acyl-CoA dehydrogenase deficiency, a condition characterized by lethargy, seizures, and hypoketotic hypoglycemia following a period

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deficiency, a condition characterized by lethargy, seizures, and hypoketotic hypoglycemia following a period of fasting.

(Choice E) A phenylalanine-free diet is recommended in patients with phenylketonuria (phenylalanine hydroxylase deficiency). Failure to convert phenylalanine to tyrosine leads to accumulation of phenylalanine and intellectual disability if the condition is left untreated.

(Choice G) Pyridoxine (vitamin B_6) can be used to treat homocystinuria, which is caused by a defect in vitamin B_6-dependent cystathionine synthase. This condition is characterized by elevated homocysteine levels, ectopia lentis, intellectual disability, Marfanoid body habitus, and increased occurrence of thromboembolic events.

Educational objective:
Ornithine transport into mitochondria is necessary for proper function of the urea cycle, which is the major disposal pathway for waste nitrogen generated by catabolism of amino acids. Urea cycle defects typically cause neurological damage due to the accumulation of ammonia. Protein restriction improves this condition by reducing the amount of amino acid turnover.

References

- The hyperornithinemia-hyperammonemia-homocitrullinuria syndrome.

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www.ncbi.nlm.nih.gov/pubmed/25874378

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A 2-year-old boy is brought to the emergency department with fever, vomiting, and sleepiness. He had several episodes of emesis this morning, and his mother was unable to wake him from his afternoon nap. The boy has had mild rhinorrhea and fever for the past 3 days. Since the newborn period, the parents say that the patient has had multiple illnesses characterized by vomiting and sleepiness. Prior laboratory testing revealed increased blood ammonia levels during these episodes and markedly increased orotic acid excretion in the urine. Physical examination shows a tachypneic boy who is unresponsive to all stimuli. Which of the following enzymes is most likely to be deficient in this patient?

A. Carbamoyl phosphate synthetase I
B. Hypoxanthine-guanine phosphoribosyltransferase
C. N-acetylglutamate synthetase
D. Ornithine transcarbamylase
E. Uridine monophosphate synthetase

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- A. Carbamoyl phosphate synthetase I (15%)
- B. Hypoxanthine-guanine phosphoribosyltransferase (4%)
- C. N-acetylglutamate synthetase (3%)
- D. Ornithine transcarbamylase (64%)
- E. Uridine monophosphate synthetase (11%)

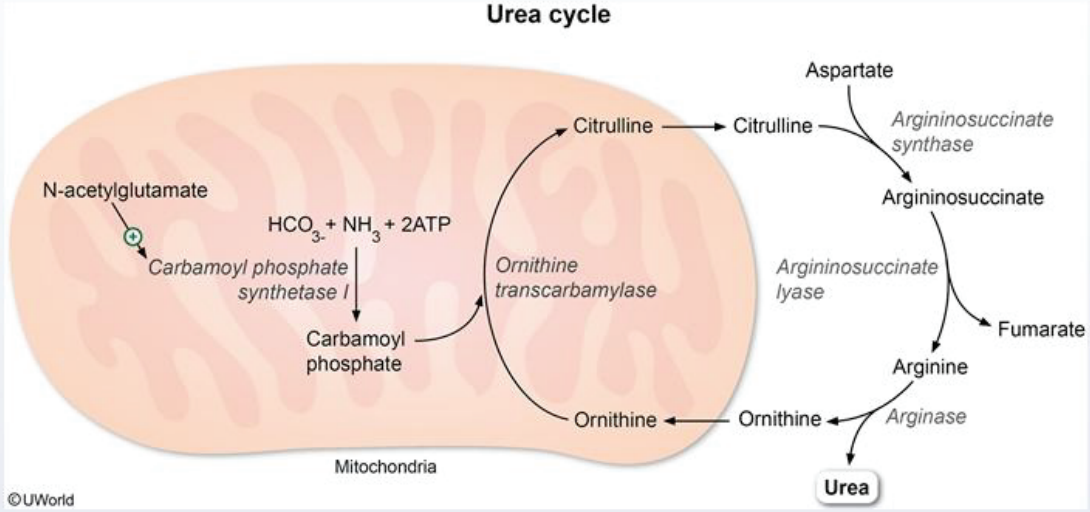
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Ammonia generated from the metabolism of amino acids is converted into urea by the urea cycle. The combination of bicarbonate (HCO_3-), ammonia, and ATP is catalyzed by carbamoyl phosphate synthetase (rate-limiting enzyme in the urea cycle) to yield carbamoyl phosphate. Carbamoyl phosphate combines with ornithine to form citrulline in a reaction catalyzed by ornithine transcarbamylase. Citrulline enters the cytosol and is converted to argininosuccinate, which is then converted to arginine. The conversion of arginine to ornithine by arginase completes the urea cycle by releasing a urea molecule.

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arginine to ornithine by arginase completes the urea cycle by releasing a urea molecule. N-acetylglutamate serves as a regulator of the urea cycle through activation of carbamoyl phosphate synthetase I.

This patient most likely has **ornithine transcarbamylase (OTC) deficiency**, the most common urea cycle disorder. OTC deficiency results in excess carbamoyl phosphate, which stimulates pyrimidine synthesis. As an intermediate product in this pathway, orotic acid accumulates and results in **increased urinary orotic acid**.

Patients also have **hyperammonemia** due to impaired ammonia excretion, which is a **metabolic emergency**. Ammonia is neurotoxic and causes **episodes of vomiting and confusion/coma**. **Tachypnea** also occurs due to cerebral edema from ammonia buildup, resulting in central hyperventilation and respiratory alkalosis. Metabolic decompensation is often triggered by illness (eg, viral upper respiratory infection, acute otitis media), fasting, or increased protein intake.

(Choices A and C) Although defects in carbamoyl phosphate synthetase I and N-Acetylglutamate synthetase also result in hyperammonemia, levels of carbamoyl phosphate are low and orotic acid is not elevated in the urine.

(Choice B) Hypoxanthine-guanine phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome) results

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synthetase also result in hyperammonemia, levels of carbamoyl phosphate are low and orotic acid is not elevated in the urine.

(Choice B) Hypoxanthine-guanine phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome) results in hyperuricemia because purines cannot be salvaged from degraded DNA. Urate kidney stones and self-mutilation are classic clinical manifestations.

(Choice E) Uridine monophosphate synthetase (UMPS) is part of the pyrimidine synthesis pathway. UMPS deficiency leads to orotic acid buildup (similar to OTC deficiency) but not hyperammonemia. Characteristic findings include megaloblastic anemia and delayed growth.

Educational objective:

Patients with urea cycle disorders typically have discrete episodes of vomiting, tachypnea, and confusion/coma secondary to hyperammonemia (a metabolic emergency). Ornithine transcarbamylase deficiency is the most common disorder of the urea cycle and is characterized by hyperammonemia and elevated urinary orotic acid.

References

- Ornithine Transcarbamylase Deficiency.
- Urea Cycle Disorders Overview.

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A research scientist studying the metabolic pathways that contribute to obesity feeds experimental animals a high-carbohydrate, high-protein diet for a prolonged period. A sample of liver tissue is then obtained from the animals, and the activity of various enzymes involved in fatty acid metabolism is measured and recorded. It is determined that beta-oxidation of fatty acids is inhibited within these cells as a result of the diet. An increase in which of the following substances is most likely responsible for the observed effect?

A. Acetoacetate
B. Carnitine
C. Citrate
D. Malonyl-CoA
E. NADPH

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A research scientist studying the metabolic pathways that contribute to obesity feeds experimental animals a high-carbohydrate, high-protein diet for a prolonged period. A sample of liver tissue is then obtained from the animals, and the activity of various enzymes involved in fatty acid metabolism is measured and recorded. It is determined that beta-oxidation of fatty acids is inhibited within these cells as a result of the diet. An increase in which of the following substances is most likely responsible for the observed effect?

A. Acetoacetate (10%)
B. Carnitine (18%)
C. Citrate (18%)
D. Malonyl-CoA (38%)
E. NADPH (13%)

Correct

38%
Answered correctly

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In the **well-fed state**, the abundance of ATP in hepatocytes inhibits isocitrate dehydrogenase, leading to high levels of citrate in the mitochondria. Citrate is transferred to the cytosol via the citrate shuttle and cleaved by ATP citrate lyase to form acetyl-CoA. High citrate levels (in addition to elevated insulin caused by high carbohydrate intake) causes upregulation of **Acetyl-CoA carboxylase**. This cytosolic enzyme catalyzes the conversion of acetyl-CoA to malonyl-CoA in the rate-limiting step of de novo **fatty acid synthesis**. Fatty acid synthase then catalyzes the condensation of malonyl-CoA with acetyl-CoA to create a 4-carbon molecule that will undergo subsequent condensation reactions to form a 16-carbon fatty acid.

Beta-oxidation of fatty acids takes place primarily within the **mitochondrial matrix**. Mitochondrial membranes are impermeable to fatty acids due to their negative charge, so a specialized membrane carrier (**carnitine**) must be used to shuttle them into the matrix. **Malonyl-CoA inhibits carnitine acyltransferase**, preventing the transfer of acyl groups into the mitochondria. This inhibitory action functions to prevent the breakdown of newly synthesized fatty acids.

(Choice A) Ketone bodies (eg, acetoacetate) are a major source of fuel for muscle, brain, and cardiac tissue that are produced during times of starvation or fasting when oxaloacetate is in short supply and acetyl-CoA is in excess.

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tissue that are produced during times of starvation or fasting when oxaloacetate is in short supply and acetyl-CoA is in excess.

(Choice B) Carnitine is an amino acid that is essential for the transport of fatty acids through the mitochondrial membrane. It is a necessary component of fatty acid oxidation.

(Choice C) Citrate is an intermediate in the TCA cycle. It can be exported out of the mitochondrial matrix and into the cytosol, where it is broken down into acetyl-CoA for use in de novo fatty acid synthesis.

(Choice E) NADPH is a reducing molecule necessary for the synthesis of fatty acids. In contrast, beta-oxidation of fats produces $FADH_2$ and NADH-reducing equivalents.

Educational objective:

Cytosolic acetyl-CoA carboxylase converts acetyl-CoA to malonyl-CoA during the rate-limiting step of de novo fatty acid synthesis. Malonyl-CoA also inhibits the action of mitochondrial carnitine acyltransferase, thereby inhibiting beta-oxidation of newly formed fatty acids.

References

- Malonyl-CoA: the regulator of fatty acid synthesis and oxidation.

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A healthy 34-year-old coal mine worker is trapped underground following partial collapse of an access shaft. Rescue efforts are directed toward clearing the obstructed tunnel, but it takes 2 days to reach him. While being taken to the surface, the miner tells rescuers that he feels dizzy and weak. He had an emergency supply of water but has not eaten anything for over 30 hours. Fingerstick blood glucose concentration is 78 mg/dL. Which of the following biochemical reactions is most likely responsible for maintaining this patient's current blood glucose levels?

A. Acetoacetyl CoA → 3-hydroxy-3-methylglutaryl-CoA
B. Acetyl CoA → palmitic acid
C. Fructose 6-phosphate → fructose 1,6-bisphosphate
D. Glycogen → glucose-1-phosphate
E. Oxaloacetate → phosphoenolpyruvate

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A. Acetoacetyl CoA → 3-hydroxy-3-methylglutaryl-CoA (13%)
B. Acetyl CoA → palmitic acid (7%)
C. Fructose 6-phosphate → fructose 1,6-bisphosphate (3%)
D. Glycogen → glucose-1-phosphate (25%)
✓ E. Oxaloacetate → phosphoenolpyruvate (50%)

Correct

50%
Answered correctly

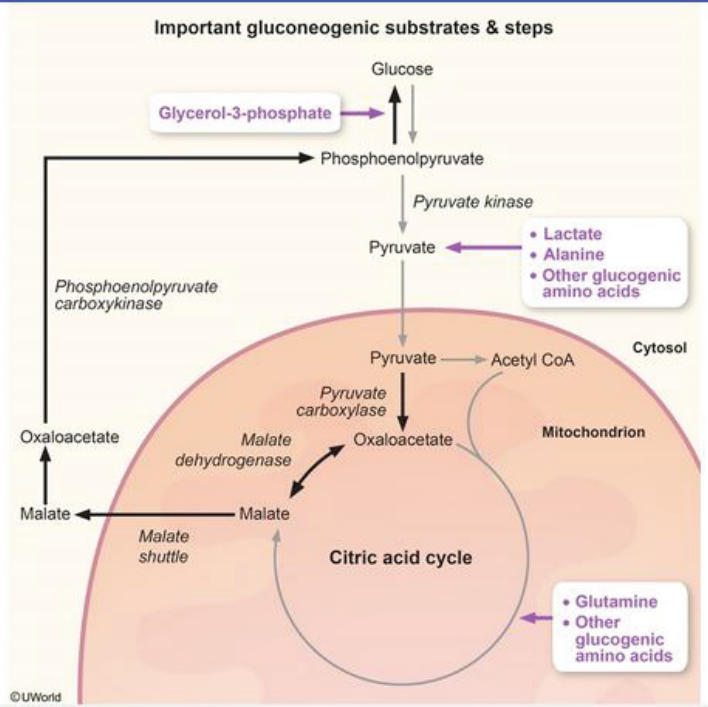
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The 2 major processes that maintain plasma glucose between meals are glycogenolysis and gluconeogenesis. Glycogenolysis is the primary source of glucose for the first 12-18 hours of fasting. Once hepatic glycogen stores become depleted, **gluconeogenesis** becomes the major process used by the body to keep blood glucose levels within the normal range. During gluconeogenesis, glucose is formed from lactate, glycerol, and glucogenic amino acids. This process uses many of the enzymes involved in glycolysis. However, hexokinase, phosphofructokinase, and pyruvate kinase are unidirectional and must be **bypassed** by distinct gluconeogenic enzymes.

The first committed step of gluconeogenesis is the biotin-dependent carboxylation of pyruvate to oxaloacetate by mitochondrial **pyruvate carboxylase**. Oxaloacetate is subsequently converted to malate by malate dehydrogenase to facilitate exit from the mitochondria, and then is converted back to oxaloacetate by cytosolic malate dehydrogenase (malate shuttle). In the cytosol, **phosphoenolpyruvate carboxykinase** (PEPCK) converts oxaloacetate to phosphoenolpyruvate. Therefore, pyruvate carboxylase and PEPCK work together to bypass pyruvate kinase. The 2 other unique gluconeogenic enzymes are **fructose 1,6-bisphosphatase** (bypasses phosphofructokinase) and **glucose-6-phosphatase** (bypasses hexokinase).

(Choice A) Conversion of acetoacetyl-CoA to 3-hydroxy-3-methylglutaryl-CoA occurs during the synthesis of cholesterol and ketone bodies. Ketone body synthesis is increased in starvation situations, however,

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hexokinase).

(Choice A) Conversion of acetoacetyl-CoA to 3-hydroxy-3-methylglutaryl-CoA occurs during the synthesis of cholesterol and ketone bodies. Ketone body synthesis is increased in starvation situations, however, ketone bodies cannot be used to synthesize glucose.

(Choice B) Palmitic acid is the first fatty acid produced from acetyl CoA during lipogenesis in the fed state. However, during prolonged fasting, lipolysis predominates and leads to generation of glycerol and fatty acids.

(Choice C) Conversion of fructose 6-phosphate to fructose 1,6-bisphosphate occurs during glycolysis and is catalyzed by phosphofructokinase. During starvation, glycolysis is minimized and gluconeogenesis predominates.

(Choice D) The first step of glycogenolysis is breakage of 1-4 glycosidic linkage to form glucose-1-phosphate. After 24 hours of fasting, maintenance of blood glucose levels is achieved mostly through gluconeogenesis, not by glycogenolysis.

Educational objective:
After 12-18 hours of fasting, gluconeogenesis becomes the principal source of blood glucose. Gluconeogenesis uses many glycolytic enzymes, but hexokinase, phosphofructokinase, and pyruvate

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fatty acids.

(Choice C) Conversion of fructose 6-phosphate to fructose 1,6-bisphosphate occurs during glycolysis and is catalyzed by phosphofructokinase. During starvation, glycolysis is minimized and gluconeogenesis predominates.

(Choice D) The first step of glycogenolysis is breakage of 1-4 glycosidic linkage to form glucose-1-phosphate. After 24 hours of fasting, maintenance of blood glucose levels is achieved mostly through gluconeogenesis, not by glycogenolysis.

Educational objective:

After 12-18 hours of fasting, gluconeogenesis becomes the principal source of blood glucose. Gluconeogenesis uses many glycolytic enzymes, but hexokinase, phosphofructokinase, and pyruvate kinase need to be bypassed as they are unidirectional. The initial steps of gluconeogenesis involve the conversion of pyruvate to oxaloacetate and oxaloacetate to phosphoenolpyruvate by pyruvate carboxylase and phosphoenolpyruvate carboxykinase, respectively.

Biochemistry	Biochemistry (General Principles)	Gluconeogenesis
Subject	System	Topic

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A 3-year-old boy is brought to the office due to abnormal motor development. He was born at 40 weeks gestation and had an unremarkable perinatal course. The boy developed normally during the first year of life. However, for the past 2 years, he has had progressive bilateral leg stiffness and abnormal involuntary movements. His cognitive and motor development is also delayed. There is no significant family history of neurological or muscular disorders. The patient's height, weight, and head circumference are below the 3rd percentile. Examination shows bilateral spastic paresis of his lower extremities and frequent choreoathetoid movements. Comprehensive laboratory testing reveals significantly elevated arginine levels in plasma and cerebrospinal fluid. The deficient enzyme in this patient is normally involved in the production of which of the following?

A. γ-aminobutyric acid
B. Glutamine
C. Homocysteine
D. Orotic acid
E. Serotonin

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A. γ-aminobutyric acid
B. Glutamine
C. Homocysteine
D. Orotic acid
E. Serotonin
F. Urea

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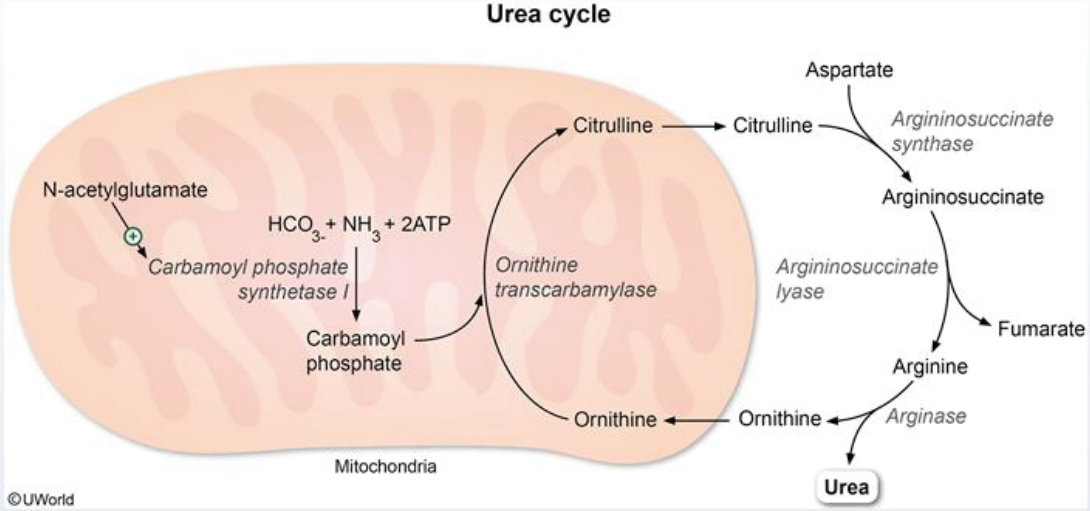
movements. His cognitive and motor development is also delayed. There is no significant family history of neurological or muscular disorders. The patient's height, weight, and head circumference are below the 3rd percentile. Examination shows bilateral spastic paresis of his lower extremities and frequent choreoathetoid movements. Comprehensive laboratory testing reveals significantly elevated arginine levels in plasma and cerebrospinal fluid. The deficient enzyme in this patient is normally involved in the production of which of the following?

A. γ-aminobutyric acid (18%)
B. Glutamine (9%)
C. Homocysteine (7%)
D. Orotic acid (11%)
E. Serotonin (2%)
F. Urea (50%)

Correct

50%
25 secs
02/05/2021

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This patient has features of **arginase deficiency**, including progressive development of **spastic diplegia**, **abnormal movements**, and growth delay in the setting of **elevated arginine levels**. Arginase is a urea cycle enzyme that produces **urea and ornithine** from arginine. Diagnosis is based on elevated arginine levels on plasma amino acid testing. Treatment of arginase deficiency consists of a **low-protein diet** devoid of arginine. Administration of a synthetic protein made of essential amino acids usually results in a dramatic decrease in plasma arginine concentration and an improvement in neurological abnormalities.

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dramatic decrease in plasma arginine concentration and an improvement in neurological abnormalities. Unlike other urea cycle disorders, patients with arginase deficiency have **mild or no hyperammonemia**.

(Choice A) The amino acid derivative γ-aminobutyrate (GABA) is a well-known inhibitor of presynaptic transmission in the retina and central nervous system. GABA is formed from glutamate decarboxylation, a reaction catalyzed by glutamate decarboxylase.

(Choice B) Glutamine is the major amino acid in the blood because it transports excess ammonia from peripheral tissues to the kidney. In the nephron, the amide nitrogen is hydrolyzed by glutaminase to regenerate glutamate and a free ammonium ion, which can then be excreted in the urine.

(Choice C) Deficiencies of vitamins B_6, B_{12}, and folate (B_9) are associated with hyperhomocysteinemia, which in turn is associated with atherosclerosis and thrombotic events.

(Choice D) Orotic acid is overproduced when a block in the urea cycle leads to excess carbamoyl phosphate, which is metabolized by dihydroorotate dehydrogenase to orotic acid. Excessive amounts of orotic acid are usually found in citrullinemia and ornithine transcarbamylase deficiency. These urea cycle disorders are also accompanied by hyperammonemia.

(Choice E) Serotonin (5-hydroxytryptamine) is formed by the hydroxylation and decarboxylation of tryptophan by tryptophan hydroxylase. In addition, serotonin is degraded by monoamine oxidase and also

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(Choice C) Deficiencies of vitamins B_6, B_{12}, and folate (B_9) are associated with hyperhomocysteinemia, which in turn is associated with atherosclerosis and thrombotic events.

(Choice D) Orotic acid is overproduced when a block in the urea cycle leads to excess carbamoyl phosphate, which is metabolized by dihydroorotate dehydrogenase to orotic acid. Excessive amounts of orotic acid are usually found in citrullinemia and ornithine transcarbamylase deficiency. These urea cycle disorders are also accompanied by hyperammonemia.

(Choice E) Serotonin (5-hydroxytryptamine) is formed by the hydroxylation and decarboxylation of tryptophan by tryptophan hydroxylase. In addition, serotonin is degraded by monoamine oxidase and also undergoes neuronal reuptake.

Educational objective:
Arginase is a urea cycle enzyme that produces urea and ornithine from arginine. Arginase deficiency results in progressive spastic diplegia, growth delay, and abnormal movements. Treatment includes an arginine-free, low-protein diet.

References

- Arginase-1 deficiency.

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Erythroblasts isolated from a bone marrow biopsy sample of a patient with neonatal jaundice are incubated in a medium containing radiolabeled glucose. The cells are unable to generate NADPH from glucose metabolism but are able to convert fructose-6-phosphate to ribose-5-phosphate, which is required for nucleic acid synthesis. Which of the following enzymes is essential for the latter conversion?

A. Aconitase
B. Enolase
C. Glucose-6-phosphate dehydrogenase
D. Glutathione reductase
E. Transketolase

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Erythroblasts isolated from a bone marrow biopsy sample of a patient with neonatal jaundice are incubated in a medium containing radiolabeled glucose. The cells are unable to generate NADPH from glucose metabolism but are able to convert fructose-6-phosphate to ribose-5-phosphate, which is required for nucleic acid synthesis. Which of the following enzymes is essential for the latter conversion?

A. Aconitase (3%)
B. Enolase (11%)
C. Glucose-6-phosphate dehydrogenase (18%)
D. Glutathione reductase (7%)
E. Transketolase (59%)

Correct

59%
Answered correctly

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Explanation

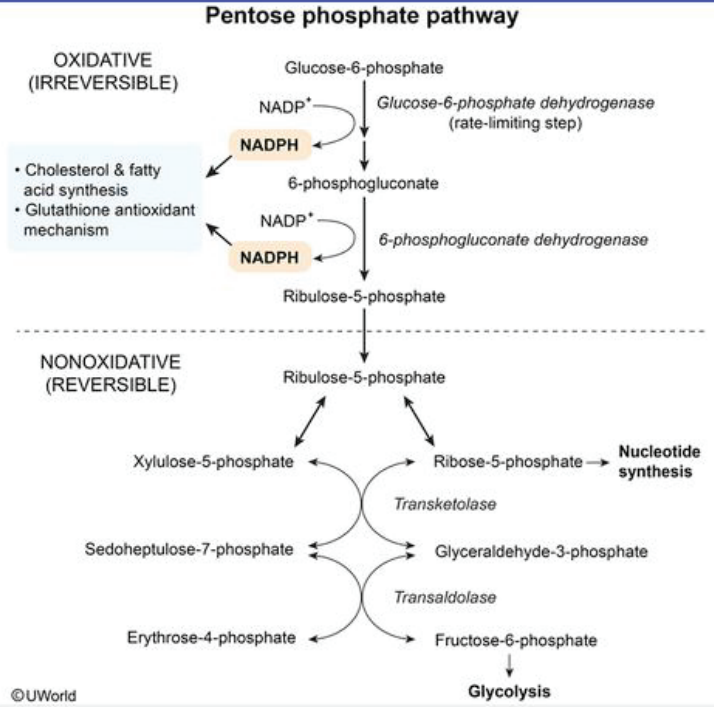
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C. Glucose-6-phosphate dehydrogenase (18%)

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Glycolysis

The **pentose phosphate pathway** (HMP shunt) generates **NADPH** for use in reductive reactions and **ribose-5-phosphate**, a precursor for the synthesis of nucleotides. The pathway consists of 2 types of reactions, oxidative (irreversible) and nonoxidative (reversible), both of which can function independently depending on cellular requirements.

Activity of the nonoxidative reactions is governed by the cellular demand for ribose-5-phosphate. When ribose-5-phosphate is produced in excess, transketolase and transaldolase can produce the **glycolytic intermediates** glyceraldehyde-3-phosphate and fructose-6-phosphate for ATP generation. When ribose-5-phosphate demand exceeds the production capabilities of the oxidative pathway, the nonoxidative pathway functions in **reverse** and transketolase and transaldolase catalyze the conversion of fructose-6-phosphate and glycerldehyde-3-phosphate to ribose-5-phosphate.

(Choice A) Aconitase catalyzes the isomerization of citrate to isocitrate in the citric acid cycle.

(Choice B) Enolase catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate in glycolysis.

(Choice C) Glucose-6-phosphate dehydrogenase catalyzes the initial and rate-limiting step of the pentose phosphate pathway. Deficiency of this enzyme results in hemolytic anemia due to the inability to generate

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(Choice C) Glucose-6-phosphate dehydrogenase catalyzes the initial and rate-limiting step of the pentose phosphate pathway. Deficiency of this enzyme results in hemolytic anemia due to the inability to generate NADPH in the oxidative portion of the pathway. However, nonoxidative reactions are responsible for conversion of fructose-6-phosphate to ribose-5-phosphate.

(Choice D) Glutathione reductase catalyzes the reduction of glutathione disulfide to glutathione using NADPH. Glutathione aids red blood cells in resisting oxidative stress.

Educational objective:

The pentose phosphate pathway consists of an oxidative (irreversible) branch and a nonoxidative (reversible) branch, and each can function independently based on cellular requirements. Transketolase, an enzyme of the nonoxidative branch, is responsible in part for the interconversion of ribose-5-phosphate (nucleotide precursor) and fructose-6-phosphate (glycolytic intermediate).

References

- The pentose phosphate pathway and cancer.

Biochemistry	Biochemistry (General Principles)	G6PD deficiency
Subject	System	Topic

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A 3-year-old boy who recently immigrated to the United States is brought to the physician by his parents because he has not yet begun to walk or speak. Assessment of his developmental milestones shows severe intellectual disability. He dies 6 months later from refractory seizures resulting in respiratory failure. Autopsy shows pallor of the substantia nigra, locus ceruleus, and vagal nucleus dorsalis. The underlying condition responsible for this patient's death is most likely caused by a deficiency of which of the following enzymes?

A. Branched-chain ketoacid dehydrogenase
B. Dopamine hydroxylase
C. Homogentisic acid oxidase
D. Phenylalanine hydroxylase
E. Tyrosinase

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A 3-year-old boy who recently immigrated to the United States is brought to the physician by his parents because he has not yet begun to walk or speak. Assessment of his developmental milestones shows severe intellectual disability. He dies 6 months later from refractory seizures resulting in respiratory failure. Autopsy shows pallor of the substantia nigra, locus ceruleus, and vagal nucleus dorsalis. The underlying condition responsible for this patient's death is most likely caused by a deficiency of which of the following enzymes?

A. Branched-chain ketoacid dehydrogenase (6%)
B. Dopamine hydroxylase (23%)
C. Homogentisic acid oxidase (4%)
✓ D. Phenylalanine hydroxylase (50%)
E. Tyrosinase (15%)

Correct

50%
Answered correctly

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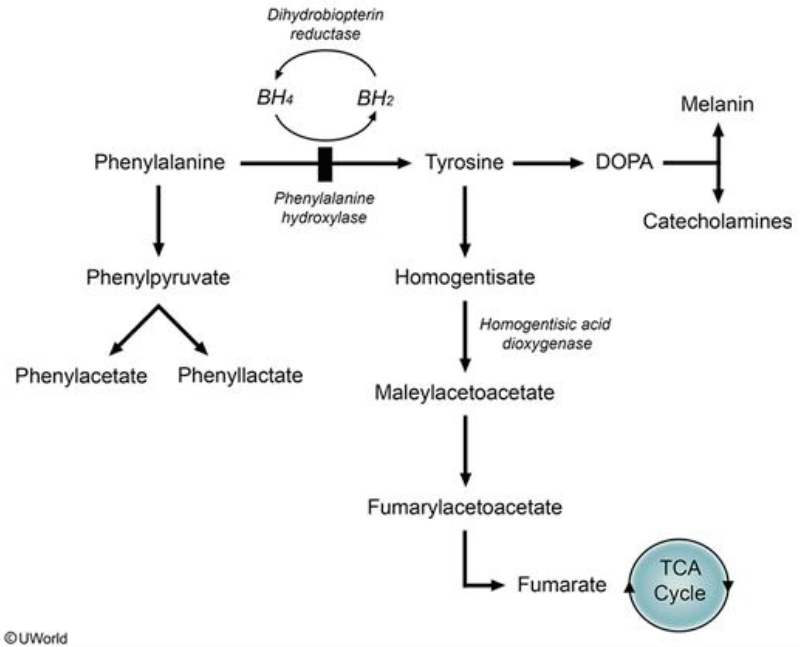
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Phenylketonuria



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This patient's severe intellectual disability, history of seizures, and abnormal pallor of catecholaminergic brain nuclei on autopsy are suggestive of phenylketonuria (PKU). PKU results from the inability to convert phenylalanine into tyrosine, a reaction which is normally catalyzed by phenylalanine hydroxylase. This enzyme requires the cofactor tetrahydrobiopterin (BH_4), which is regenerated from dihydrobiopterin (BH_2) by the enzyme dihydropteridine reductase. Although neonatal hyperphenylalaninemia can be caused by deficiency of either enzyme, most cases are attributable to abnormalities in phenylalanine hydroxylase.

It is believed that excess phenylalanine and the presence of large concentrations of phenylalanine metabolites (eg, phenyllactate & phenylacetate) contribute to the brain damage seen in PKU. Hypopigmentation involving the skin, hair, eyes, and catecholaminergic brain nuclei (which produce a dark pigment known as neuromelanin) results from the inhibitory effect of excess phenylalanine on melanin synthesis. The classic musty or mousy body odor is due to the accumulation of abnormal phenylalanine metabolites.

(Choice A) Branched-chain ketoacid dehydrogenase catalyzes decarboxylation of the α-ketoacid derivatives of all 3 branched chain amino acids: leucine, isoleucine, and valine. Deficiency causes maple syrup urine disease, which is characterized by a burnt-sugar smell in the urine of affected patients.

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Phenylketonuria	
Pathophysiology	• Autosomal recessive mutation in phenylalanine hydroxylase • Failure to convert phenylalanine into tyrosine results in hyperphenylalaninemia & neurologic injury
Clinical features	• Severe intellectual disability • Seizures • Musty body odor • Hypopigmentation involving skin, hair, eyes & brain nuclei
Diagnosis	• Newborn screening (tandem mass spectrometry) • Quantitative amino acid analysis (↑ phenylalanine levels)
Treatment	Dietary restriction of phenylalanine

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(Choice A) Branched-chain ketoacid dehydrogenase catalyzes decarboxylation of the α-ketoacid derivatives of all 3 branched chain amino acids: leucine, isoleucine, and valine. Deficiency causes maple syrup urine disease, which is characterized by a burnt-sugar smell in the urine of affected patients. Hypopigmentation is not seen in the condition.

(Choice B) Dopamine hydroxylase is the enzyme that catalyzes the biosynthesis of norepinephrine from dopamine. Deficiency of this enzyme causes a rare form of dysautonomia characterized by ptosis, orthostatic hypotension, hypoglycemia, and hypothermia.

(Choice C) Alkaptonuria is an autosomal recessive disorder of tyrosine degradation caused by a deficiency of homogentisic acid oxidase. This condition results in the accumulation of large amounts of homogentisic acid, leading to connective tissue hyperpigmentation and degenerative joint disease.

(Choice E) Albinism is an autosomal recessive disorder caused by defects in the biosynthesis and distribution of melanin. It is most commonly due to depressed or absent tyrosinase activity. Melanin synthesis begins with the conversion of tyrosine to DOPA and DOPA to dopaquinone by the enzyme tyrosinase in melanocytes. Albinism does not present with neurologic dysfunction.

Educational objective:
Deficiency of the enzyme phenylalanine hydroxylase or its cofactor tetrahydrobiopterin causes

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orthostatic hypotension, hypoglycemia, and hypothermia.

(Choice C) Alkaptonuria is an autosomal recessive disorder of tyrosine degradation caused by a deficiency of homogentisic acid oxidase. This condition results in the accumulation of large amounts of homogentisic acid, leading to connective tissue hyperpigmentation and degenerative joint disease.

(Choice E) Albinism is an autosomal recessive disorder caused by defects in the biosynthesis and distribution of melanin. It is most commonly due to depressed or absent tyrosinase activity. Melanin synthesis begins with the conversion of tyrosine to DOPA and DOPA to dopaquinone by the enzyme tyrosinase in melanocytes. Albinism does not present with neurologic dysfunction.

Educational objective:
Deficiency of the enzyme phenylalanine hydroxylase or its cofactor tetrahydrobiopterin causes accumulation of phenylalanine in body fluids and the central nervous system. Homozygous infants are normal at birth but gradually develop severe intellectual disability and seizures if left untreated. Hypopigmentation of the skin, hair, eyes, and catecholaminergic brain nuclei is also frequently seen.

Biochemistry	Biochemistry (General Principles)	Phenylketonuria
Subject	System	Topic

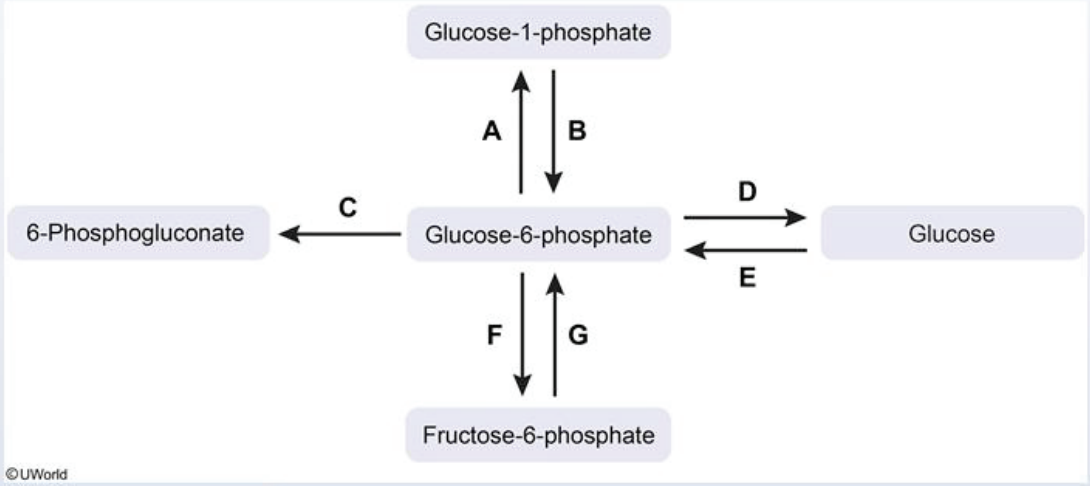
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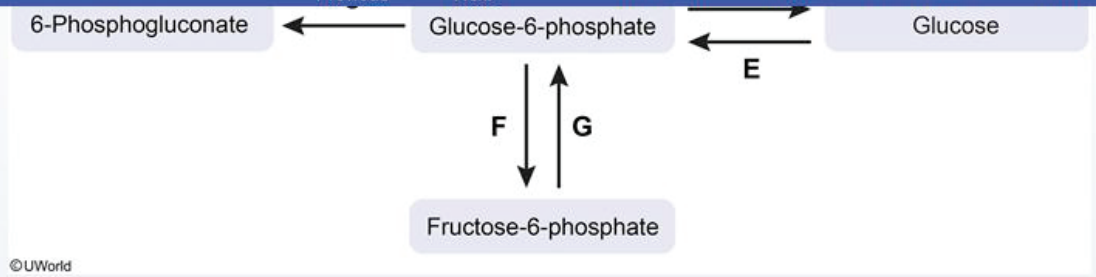
A 20-year-old man is evaluated in the emergency department for weakness, malaise, and dark urine. The patient was treated for a bacterial skin infection several days ago. Physical examination shows scleral icterus. Laboratory results reveal anemia with an elevated reticulocyte count. Abnormal erythrocytes are seen on peripheral smear. Which of the following substrate flow pathways is most likely deficient in this patient?



A. A

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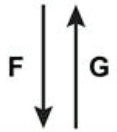


- A. A
- B. B
- C. C
- D. D
- E. E
- F. F
- G. G

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Fructose-6-phosphate

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- A.A (7%)
- B.B (5%)
- C.C (57%)
- D.D (11%)
- E.E (5%)
- F. F (9%)
- G.G (2%)

Correct

57%

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11/23/2020

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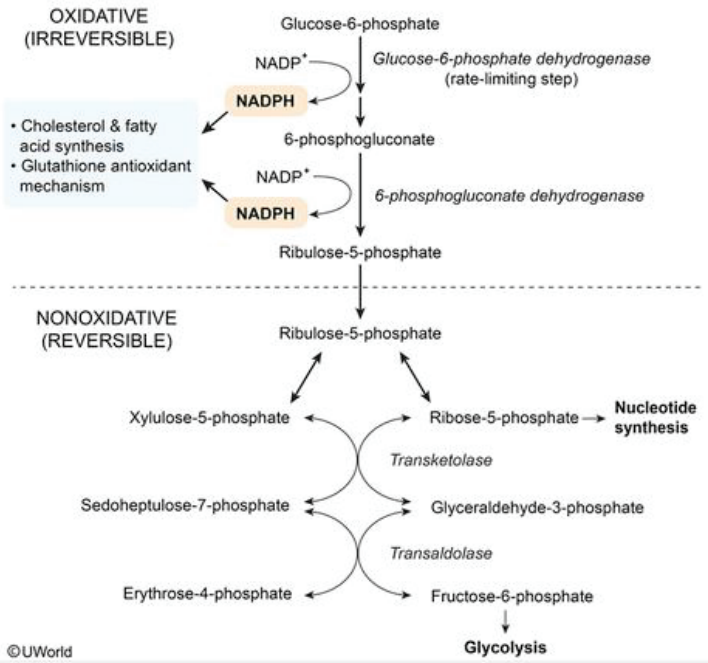
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OXIDATIVE

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Pentose phosphate pathway



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Transaldolase

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This patient is likely suffering from **glucose-6-phosphate dehydrogenase (G6PD)** deficiency, an X-linked recessive disorder resulting in episodic bouts of hemolysis when red blood cells experience increased oxidative stress.

G6PD is the rate-limiting enzyme of the **pentose phosphate pathway (PPP)**. This enzyme catalyzes the conversion of glucose-6-phosphate to 6-phosphogluconolactone, which is subsequently converted to 6-phosphogluconate. The PPP serves to generate both **NADPH** and **ribose-5-phosphate**, a precursor for nucleotide synthesis. Red blood cells utilize reduced NADPH to maintain a steady supply of **glutathione**, a molecule capable of neutralizing free radicals and therefore protecting the cells against oxidative damage. As the PPP is the only mechanism for red blood cells to generate NADPH, enzymatic defects in the pathway increase their susceptibility to oxidative damage.

Increased **oxidative stress** can occur as a result of exposure to medications (eg, antimalarials, sulfonamides), certain foods (eg, fava beans), and infection. This patient was likely treated with a sulfonamide drug for his bacterial skin infection, which precipitated hemolytic anemia. Oxidative damage to red blood cells also causes hemoglobin to denature, forming insoluble Heinz bodies that are removed in the spleen (produces characteristic **bite cells**).

(Choices A and B) Phosphoglucomutase interconverts glucose-6-phosphate and glucose-1-phosphate.

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(Choices A and B) Phosphoglucomutase interconverts glucose-6-phosphate and glucose-1-phosphate. This enzyme links glycogenolysis, glycogenesis, and glycolysis.

(Choice D) This reaction is the final step in both gluconeogenesis and glycogenolysis in the liver. It is catalyzed by glucose-6-phosphatase and results in the liberation of a free glucose molecule. Enzyme deficiency results in glycogen storage disease type I.

(Choice E) This reaction is the first step in glycolysis and is catalyzed by hexokinase or glucokinase. Hexokinase deficiency is a rare cause of hemolytic anemia, and glucokinase deficiency has been linked to hyperglycemic states and diabetes.

(Choices F and G) Interconversion of glucose-6-phosphate and fructose-6-phosphate is catalyzed by the bidirectional enzyme phosphoglucose isomerase. Enzyme deficiency is responsible for a small percentage of hemolytic anemias.

Educational objective:
Glucose-6-phosphate dehydrogenase (G6PD) is the rate-limiting enzyme of the pentose phosphate pathway. G6PD deficiency is a common X-linked recessive disorder resulting in episodes of hemolytic anemia during times of increased oxidative stress (eg, use of antimalarials/sulfonamide, infections).

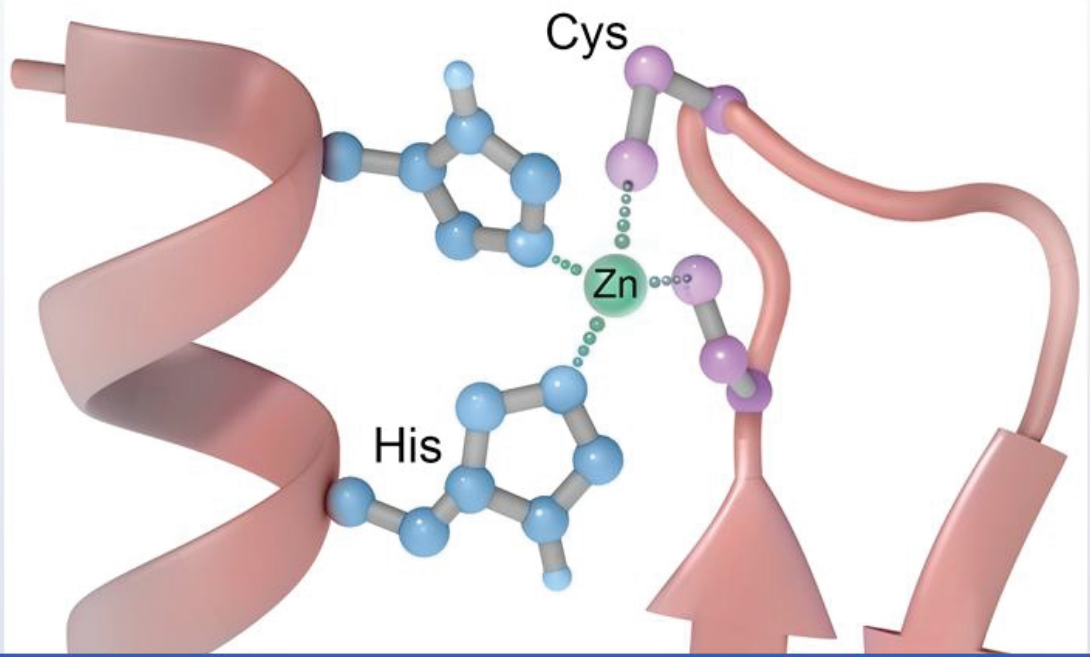
References

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A researcher is studying the structure of different hormone receptors. Receptor proteins are isolated and purified from a homogenized tissue sample. Detailed structural analysis shows that one of the proteins contains a 30-amino acid motif coordinating a zinc molecule, as shown in the image below.

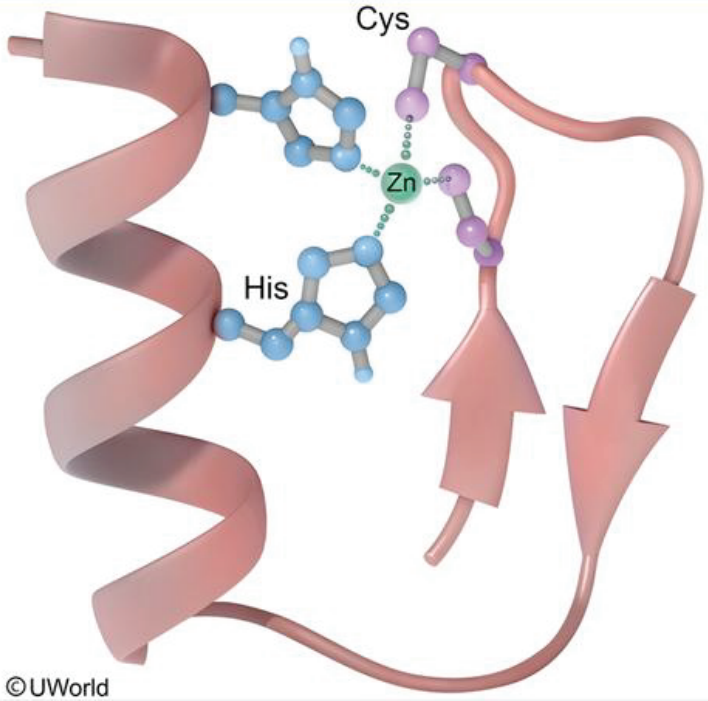


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A receptor for which of the following hormones was most likely isolated in this experiment?

- A. Adrenocorticotropic hormone
- B. Antidiuretic hormone
- C. Epinephrine
- D. Glucagon
- E. Growth hormone
- F. Insulin
- G. Thyroid hormone

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A receptor for which of the following hormones was most likely isolated in this experiment?

- A. Adrenocorticotropic hormone (11%)
- B. Antidiuretic hormone (5%)
- C. Epinephrine (5%)
- D. Glucagon (6%)
- E. Growth hormone (20%)
- F. Insulin (16%)
- ✓ G. Thyroid hormone (34%)

Correct

34%

01 min, 18 secs

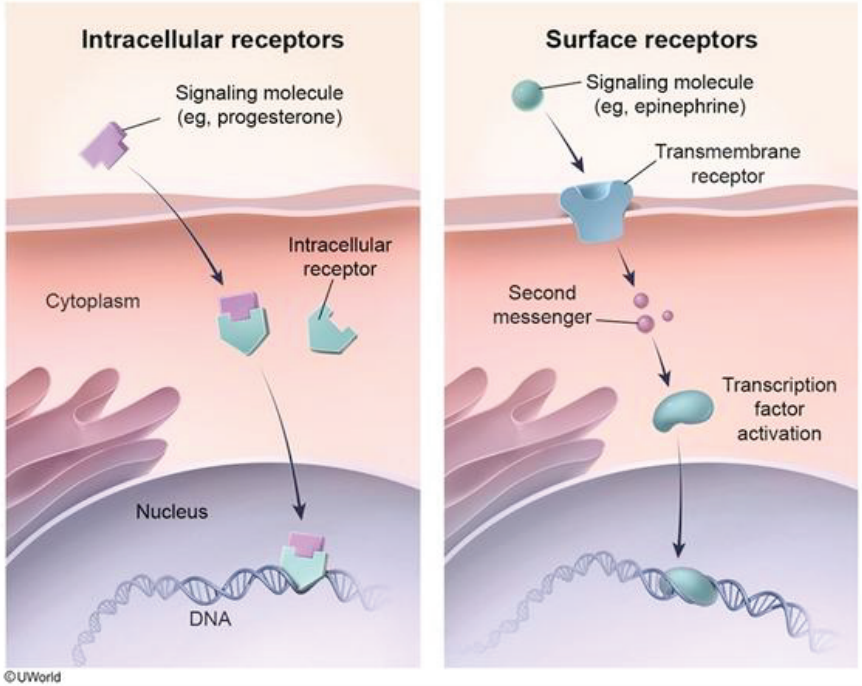
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The **zinc-finger** structure represents the most commonly identified DNA-binding domain in humans. Zinc-finger motifs are composed of chains of amino acids bound together around a zinc atom via linkages with cysteine (and sometimes histidine) residues. This forms a stable, finger-shaped structure containing 2 antiparallel β- strands and an α-helix. Unique combinations of amino acids as well as the specific histidine and cysteine linkages determine DNA-binding specificity. Many transcription factors use multiple zinc-finger motifs to recognize specific genes and alter their activity.

Although most hormones alter transcription regulation to some degree in target cells, only **intracellular receptors** located in the cytoplasm or nucleus can **act directly as transcription factors**. These intracellular receptors typically bind **lipid-soluble hormones** because the ligand has to diffuse across the cell membrane to reach the receptor. Once bound to their ligand, these receptors bind directly to target DNA sequences via zinc fingers to regulate gene expression. Examples include steroid (eg, estrogen, aldosterone, cortisol), **thyroid hormone**, and fat-soluble vitamin receptors.

In contrast, non-lipid-soluble hormones interact with transmembrane receptors found on the cell membrane. These receptors use a signal transduction cascade involving second messengers with subsequent activation of non-receptor-associated transcription factors; they do not contain DNA-binding domains. Examples include the G-protein-coupled receptors that bind ACTH, ADH, epinephrine, and glucagon **(Choices A, B, C, and D)** as well as receptors with intrinsic and associated tyrosine kinase

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DNA sequences via zinc fingers to regulate gene expression. Examples include steroid (eg, estrogen, aldosterone, cortisol), **thyroid hormone**, and fat-soluble vitamin receptors.

In contrast, non-lipid-soluble hormones interact with transmembrane receptors found on the cell membrane. These receptors use a signal transduction cascade involving second messengers with subsequent activation of non-receptor-associated transcription factors; they do not contain DNA-binding domains. Examples include the G-protein-coupled receptors that bind ACTH, ADH, epinephrine, and glucagon **(Choices A, B, C, and D)** as well as receptors with intrinsic and associated tyrosine kinase activity (eg, insulin and growth hormone receptors, respectively) **(Choices E and F)**.

Educational objective:

Zinc-finger motifs are composed of chains of amino acids bound together around a zinc atom via linkages with cysteine and histidine residues. They recognize specific DNA sequences and are used by many transcription factors to bind DNA and alter activity of target genes. Intracellular receptors that bind steroids, thyroid hormone, and fat-soluble vitamins act directly as transcription factors and contain zinc-finger binding domains.

References

- The prokaryotic zinc-finger: structure, function and comparison with the eukaryotic counterpart.

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A 68-year-old man comes to the office due to an enlarging mole on his right forearm. The patient is a retired farmer and received a significant amount of sun exposure over the course of his life. On examination, he has a black-brown macular lesion on the dorsum of his right forearm measuring approximately 1 cm in diameter with an irregular border. Excisional biopsy is performed and histopathology reveals malignant melanoma. Immunohistochemical analysis indicates that the malignant cells have decreased integrin expression. These cells are most likely to exhibit poor adhesion to which of the following components of the extracellular matrix?

A. Actin
B. Fibronectin
C. Hyaluronic acid
D. Keratan sulfate
E. Keratin

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A. Actin (12%)
B. Fibronectin (48%)
C. Hyaluronic acid (13%)
D. Keratan sulfate (9%)
E. Keratin (15%)

48%
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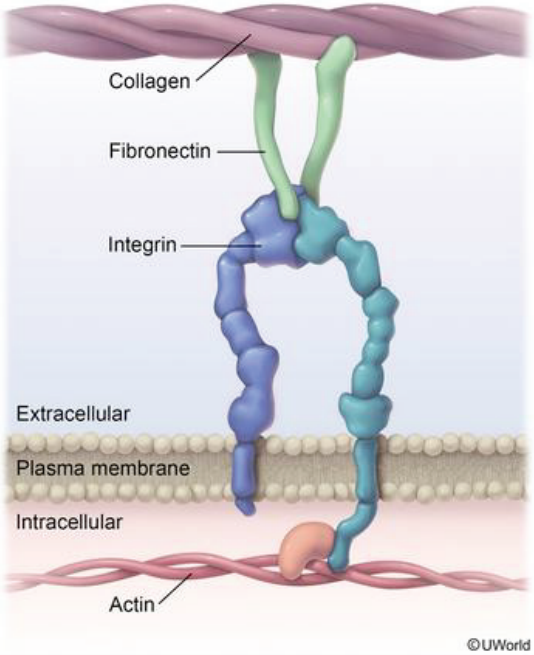
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Integrin and fibronectin



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Cellular adhesion is the means by which one cell binds to another cell, surface, or matrix. The **integrins** are a family of transmembrane protein receptors that interact with the extracellular matrix by binding to specific proteins, including collagen, fibronectin, and laminin. Other adhesion molecule classes include the cadherins, selectins, and Ig superfamily members.

Fibronectins are large glycoproteins produced by fibroblasts and some epithelial cells. Fibronectin binds to integrins, matrix collagen, and glycosaminoglycans, serving as a mediator of cell adhesion and migration. Differential expression of integrin subtypes affects adhesion properties of individual cells, and correlates with **malignant behavior** in a number of tumors, including melanoma.

(Choices A and E) The intracellular domains of the integrins interact with a number of structural proteins, including microfilaments (actin) within the cytoplasm and intermediate filaments (keratin). However, the extracellular domains do not interact with these structures.

(Choices C and D) Hyaluronic acid is a glycosaminoglycan that contributes to water retention in the extracellular matrix, and determines the stiffness of the matrix. Keratan sulfate is a glycosaminoglycan in the extracellular matrix that may play a role in maintaining type I collagen fibril organization in a number of tissues (eg, cornea). However, neither of these is a ligand for integrins.

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correlates with **malignant behavior** in a number of tumors, including melanoma.

(Choices A and E) The intracellular domains of the integrins interact with a number of structural proteins, including microfilaments (actin) within the cytoplasm and intermediate filaments (keratin). However, the extracellular domains do not interact with these structures.

(Choices C and D) Hyaluronic acid is a glycosaminoglycan that contributes to water retention in the extracellular matrix, and determines the stiffness of the matrix. Keratan sulfate is a glycosaminoglycan in the extracellular matrix that may play a role in maintaining type I collagen fibril organization in a number of tissues (eg, cornea). However, neither of these is a ligand for integrins.

Educational objective:

Adhesion of cells to the extracellular matrix involves integrin-mediated binding to fibronectin, collagen, and laminin. Differential expression of integrin subtypes affects adhesion properties of individual cells, and has been found to correlate with malignant behavior in a number of tumors.

References

- Integrins: versatile receptors controlling melanocyte adhesion, migration, and proliferation.

Subject	System	Topic
Biochemistry	Biochemistry (General Principles)	Cell adhesion molecules

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www.ncbi.nlm.nih.gov/pubmed/21087420

A 54-year-old man comes to the emergency department with a 3-month history of fatigue and exertional dyspnea. He has early satiety and frequent upper abdominal discomfort. On physical examination, the patient has palpable splenomegaly but no lymphadenopathy. Laboratory tests are as follows:

Complete blood count	
Hemoglobin	9.2 mg/dL
Platelets	80,000/mm^3
Leukocytes	56,000/mm^3

Reverse transcription polymerase chain reaction is used to diagnose chronic myelogenous leukemia in this patient. Which of the following is most likely to be detected by this test?

A. Chromosomal position of the *BCR* and *ABL* genes
B. DNA rearrangement in the *BCR* promoter region
C. Fusion protein containing BCR and ABL domains

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Hemoglobin	9.2 mg/dL
Platelets	80,000/mm^3
Leukocytes	56,000/mm^3

Reverse transcription polymerase chain reaction is used to diagnose chronic myelogenous leukemia in this patient. Which of the following is most likely to be detected by this test?

A. Chromosomal position of the *BCR* and *ABL* genes
B. DNA rearrangement in the *BCR* promoter region
C. Fusion protein containing BCR and ABL domains
D. Messenger RNA transcript containing *BCR* and *ABL* exons
E. Point mutation in the *ABL* enhancer region

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Hemoglobin	9.2 mg/dL
Platelets	80,000/mm^3
Leukocytes	56,000/mm^3

Reverse transcription polymerase chain reaction is used to diagnose chronic myelogenous leukemia in this patient. Which of the following is most likely to be detected by this test?

A. Chromosomal position of the *BCR* and *ABL* genes (26%)

B. ~~DNA rearrangement in the *BCR* promoter region~~ (10%)

C. ~~Fusion protein containing BCR and ABL domains~~ (30%)

✓ D. Messenger RNA transcript containing *BCR* and *ABL* exons (28%)

E. ~~Point mutation in the *ABL* enhancer region~~ (3%)

Correct

28%

03 mins, 09 secs

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Reverse transcription polymerase chain reaction (RT-PCR) is used to detect and quantify levels of **messenger RNA** (mRNA) in a sample. It is similar to regular PCR in that it uses sequence-specific primers, thermostable DNA polymerase, and a pool of deoxyribonucleoside triphosphates to amplify a DNA template. In RT-PCR, this template is generated by the action of **reverse transcriptase** on the mRNA sample, producing a complementary DNA (cDNA) strand that can then be amplified by PCR. Because cDNA is complementary to the mRNA sequence, it contains the **exons** of a gene along with the 5′ and 3′ untranslated regions.

Chronic myelogenous leukemia (CML) is characterized by uncontrolled proliferation of the myeloid stem cell line due to a chromosomal translocation. This translocation causes the *BCR* gene on chromosome 22 to fuse with the *ABL* gene on chromosome 9, forming the *BCR-ABL* fusion gene. The BCR-ABL fusion protein product is a constitutively active tyrosine kinase that accelerates cell division and increases genetic instability. RT-PCR can be used to identify mRNA transcribed from the *BCR-ABL* fusion gene and therefore diagnose CML.

(Choice A) Fluorescence in situ hybridization (FISH) techniques allow direct localization of genes to their respective chromosomes by using a labeled DNA probe complementary to the sequence of interest.

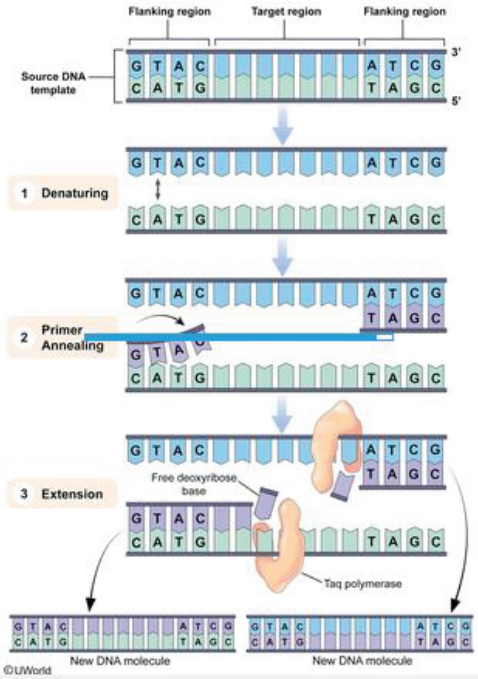
(Choices B and E) RT-PCR amplification uses an mRNA template, so it cannot detect changes in the

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Polymerase chain reaction



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(Choices B and E) RT-PCR amplification uses an mRNA template, so it cannot detect changes in the

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(Choice A) Fluorescence in situ hybridization (FISH) techniques allow direct localization of genes to their respective chromosomes by using a labeled DNA probe complementary to the sequence of interest.

(Choices B and E) RT-PCR amplification uses an mRNA template, so it cannot detect changes in the parts of the gene that are not transcribed (eg, promoter and enhancer regions). Other PCR techniques that use chromosomal DNA can detect changes in these nontranscribed regions.

(Choice C) RT-PCR is used to detect levels of mRNA expression; it does not identify proteins. A Western blot study can detect the BCR-ABL protein by using monoclonal antibodies directed against BCR or ABL.

Educational objective:
Reverse transcription polymerase chain reaction (RT-PCR) is used to detect and quantify levels of mRNA in a sample. It uses reverse transcription to create a complementary DNA template that is then amplified using the standard PCR procedure. RT-PCR can be used to diagnose chronic myelogenous leukemia by identifying an mRNA transcript containing both *BCR* and *ABL* exons in affected cells.

References

- Real time polymerase chain reaction in diagnosis of chronic myeloid leukemia.

Biochemistry	Biochemistry (General Principles)	Chronic myeloid leukemia
Subject	System	Topic

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A 78-year-old woman comes to the office due to tenderness and easy bleeding of the gums when she brushes her teeth. The patient has brushed her teeth twice a day for as long as she can remember and has not experienced these symptoms before. Physical examination shows swollen gingiva that bleed on probing. Her skin findings are shown in the image below.



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Further questioning reveals that the patient lives alone and that her diet consists primarily of tea and toast. Her symptoms are most likely caused by hypoactivity of an enzyme found in which of the following compartments?

- A. Extracellular space
- B. Golgi apparatus
- C. Lysosomes
- D. Mitochondria
- E. Nucleus
- F. Rough endoplasmic reticulum

Submit

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Further questioning reveals that the patient lives alone and that her diet consists primarily of tea and toast. Her symptoms are most likely caused by hypoactivity of an enzyme found in which of the following compartments?

A. Extracellular space (15%)
B. Golgi apparatus (14%)
C. Lysosomes (4%)
D. Mitochondria (10%)
E. Nucleus (3%)
F. Rough endoplasmic reticulum (50%)

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Disorders caused by defective collagen synthesis

Disorder	Defining characteristics	Impairment
Ehlers-Danlos syndrome (types I & II)	• Joint hypermobility • Hyperextensible, fragile skin • Most common form of EDS	Mutation in type V collagen
Osteogenesis imperfecta	• Spontaneous fractures • Bone & tooth malformation • Blue sclerae	Mutation in type I collagen
Scurvy	• Bleeding gums • Ecchymoses & petechiae • Impaired wound healing	Lack of vitamin C impairs collagen hydroxylation

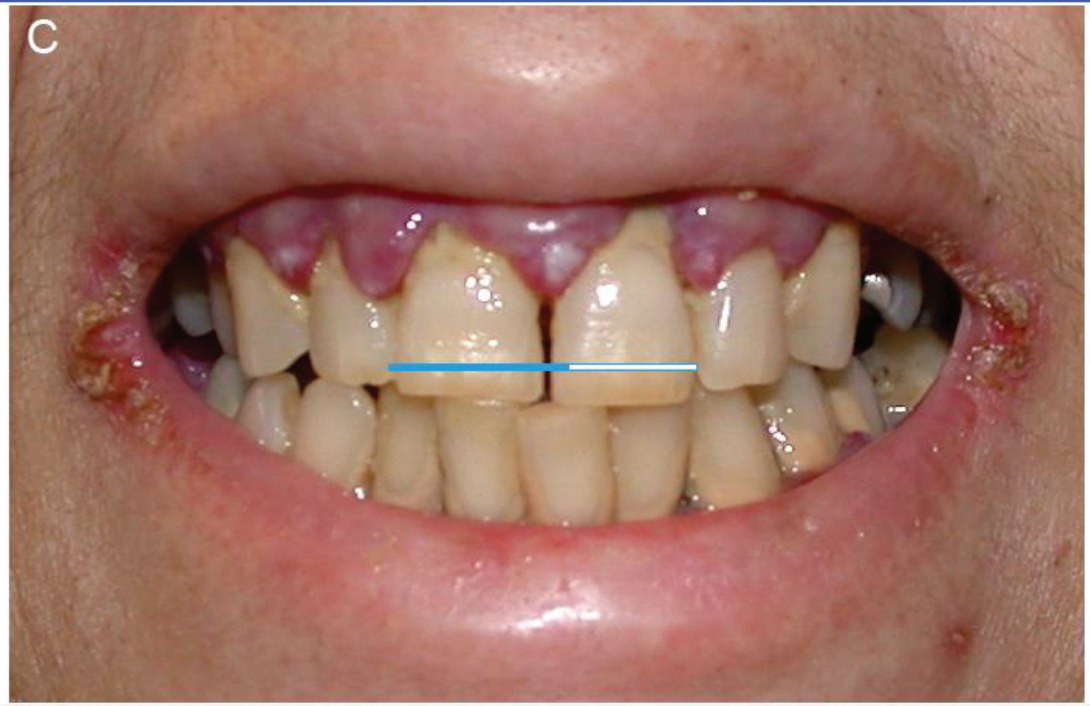
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This patient likely has **vitamin C deficiency (scurvy)**. In the United States, vitamin C deficiency is seen primarily among malnourished populations, including alcoholics, the poor, and the elderly. The symptoms of scurvy reflect impaired formation of collagen and include gingival swelling/bleeding, petechiae, ecchymoses, and poor wound healing. Perifollicular hemorrhages and coiled (corkscrew) hairs are also commonly seen.

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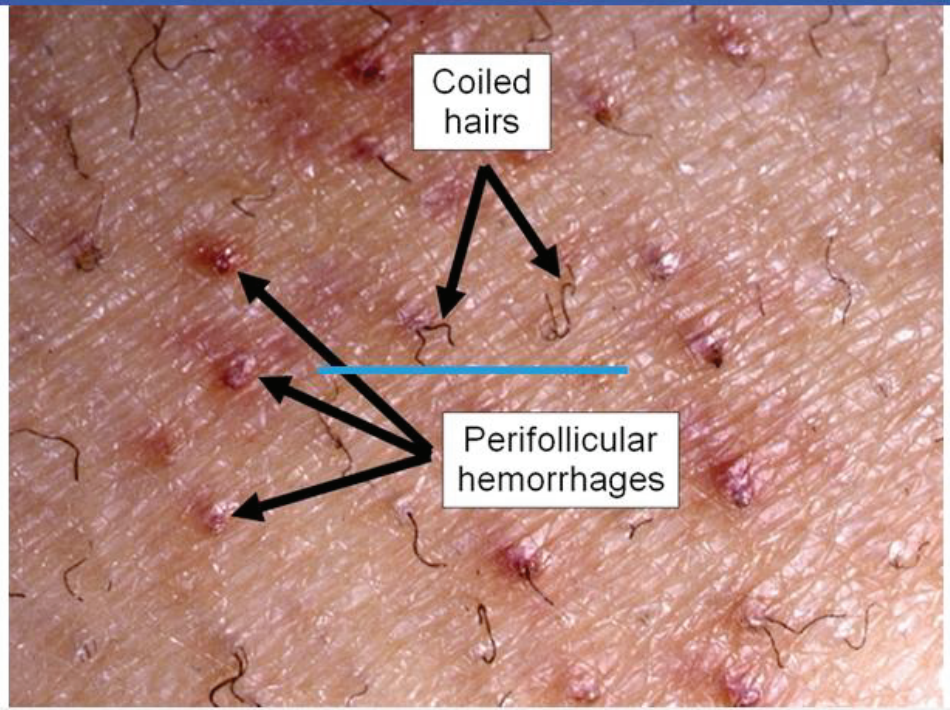


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commonly seen.

Collagen synthesis is a complex process that begins with the transcription of collagen genes in the nucleus **(Choice E)**. Collagen α-chains are then synthesized by rough endoplasmic reticulum (RER)-bound ribosomes and directed into the cisternae of the RER. Within the RER, specific **proline and lysine** residues are post-translationally **hydroxylated** to hydroxyproline and hydroxylysine by prolyl hydroxylase and lysyl hydroxylase, respectively. **Vitamin C** is a **required cofactor** for this post-translational modification. Defective hydroxylation of these residues severely diminishes the amount of collagen secreted by fibroblasts and impairs triple helix stability and covalent crosslink formation.

(Choices A and B) After formation of the triple helix, procollagen molecules are secreted from the cell via the Golgi apparatus. Propeptides at the N- and C-terminals are cleaved by extracellular procollagen peptidase to form insoluble tropocollagen molecules. These monomers then self-assemble into collagen fibrils that are subsequently crosslinked via lysyl oxidase.

(Choices C and D) Lysosomes and mitochondria are not directly involved in the synthesis of collagen.

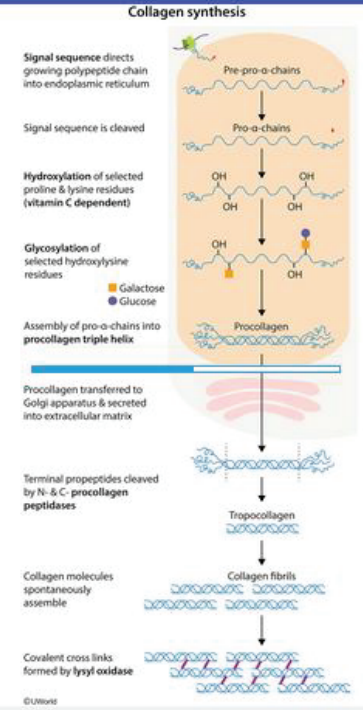
Educational objective:
The hydroxylation of proline and lysine residues in collagen helps it attain its maximum tensile strength. This process occurs in the rough endoplasmic reticulum and requires vitamin C as a cofactor. Impaired

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commonly seen.

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residues are post-translationally **hydroxylated** to hydroxyproline and hydroxylysine by prolyl hydroxylase and lysyl hydroxylase, respectively. **Vitamin C** is a **required cofactor** for this post-translational modification. Defective hydroxylation of these residues severely diminishes the amount of collagen secreted by fibroblasts and impairs triple helix stability and covalent crosslink formation.

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(Choices C and D) Lysosomes and mitochondria are not directly involved in the synthesis of collagen.

Educational objective:

The hydroxylation of proline and lysine residues in collagen helps it attain its maximum tensile strength. This process occurs in the rough endoplasmic reticulum and requires vitamin C as a cofactor. Impaired collagen synthesis resulting from vitamin C deficiency (scurvy) can lead to fragile vessels, predisposing to gingival bleeding, ecchymosis, and petechia.

References

- Be vigilant for scurvy in high-risk groups.

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Molecular biologists studying signal transduction apply an agent to human cells that activates G-protein-dependent phospholipase C. Which of the following intracellular substances is most likely to increase immediately after exposure to this agent?

A. Ca^{2+}
B. cAMP
C. cGMP
D. Cl^-
E. mRNA
F. NO

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Molecular biologists studying signal transduction apply an agent to human cells that activates G-protein-dependent phospholipase C. Which of the following intracellular substances is most likely to increase immediately after exposure to this agent?

- A. Ca^{2+} (77%)
- B. cAMP (10%)
- C. cGMP (9%)
- D. Cl^- (0%)
- E. mRNA (0%)
- F. NO (1%)

Correct

77%
Answered correctly

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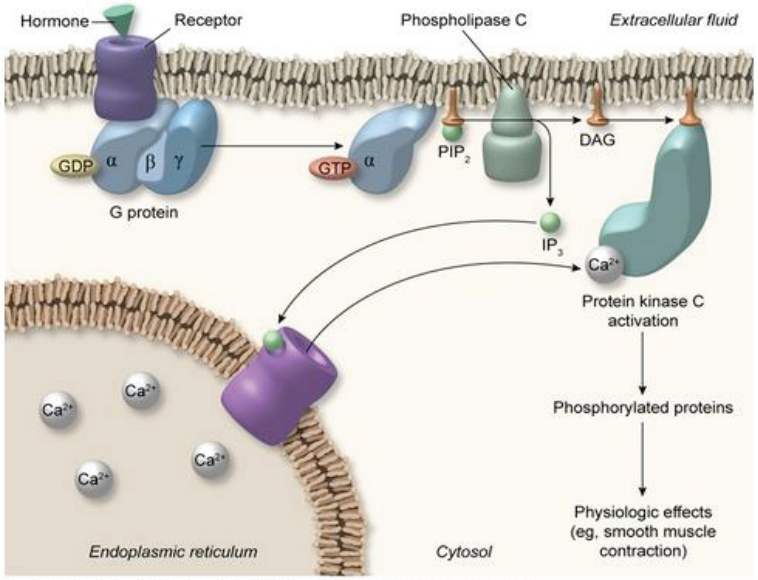
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Phosphatidylinositol 2nd messenger system



DAG = diacylglycerol; **GDP** = guanosine 5'-diphosphate; **GTP** = guanosine 5'-triphosphate; **IP_3** = inositol 1,4,5-trisphosphate; **PIP_2** = phosphatidylinositol 4,5-bisphosphate.

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A variety of hormone receptors are known to exert their intracellular effects via the **phosphoinositol system**. Examples include α_1-adrenergic, M_1 and M_3 cholinergic, V_1 (vasopressin), H_1 (histamine), oxytocin, angiotensin II, TRH, and GnRH receptors. This signal transduction pathway proceeds through the following steps:

1. Binding of a ligand to its cell surface receptor causes the **exchange of GDP for GTP** on the α-subunit of a **G_q-protein** associated with the receptor. The activated α-subunit undergoes a conformational change and exposes a **phospholipase C** (PLC) activating site.
2. After activation, PLC hydrolyzes **phosphatidyl inositol bisphosphate** (PIP_2) into **diacylglycerol** (DAG) and **inositol triphosphate** (IP_3).
3. DAG is able to directly stimulate **protein kinase C** (PKC), but the major activator of PKC is **increased intracellular Ca^{2+}** that occurs due to IP_3 mediated-release of intracellular Ca^{2+} stores from the endoplasmic reticulum. PKC is the major effector molecule in this pathway; it directly modulates the activity of other proteins via phosphorylation.

(Choices B and C) Intracellular cAMP and cGMP concentrations increase during activation of adenylate or guanylate cyclase second messenger systems, respectively. Levels can also increase following cyclic

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activity of other proteins via phosphorylation.

(Choices B and C) Intracellular cAMP and cGMP concentrations increase during activation of adenylate or guanylate cyclase second messenger systems, respectively. Levels can also increase following cyclic nucleotide phosphodiesterase inhibition, as seen on exposure to sildenafil, which selectively inhibits cGMP phosphodiesterase and results in smooth muscle relaxation in blood vessels.

(Choice D) Intracellular Cl^- concentration increases slightly after inhibitory neurotransmitters (eg, GABA, glycine) act on the neuron to increase Cl^- membrane conductance (hyperpolarization).

(Choice E) The intracellular concentration of mRNA increases during cellular states of elevated protein synthesis (eg, during cell division).

(Choice F) Nitric oxide (NO) is a paracrine signaling molecule with a lifetime of a few seconds. It can freely cross cell membranes and functions as a critical component of endothelium-mediated vasodilation. NO is synthesized from arginine and O_2 by the enzyme NO-synthase.

Educational objective:

The phosphoinositol second messenger system begins with ligand-receptor binding and G_q-protein activation leading to activation of phospholipase C (PLC). PLC then hydrolyzes phosphatidyl inositol bisphosphate and forms diacylglycerol and inositol triphosphate (IP_3). Finally, IP_3 activates protein kinase C

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glycine) act on the neuron to increase Cl^- membrane conductance (hyperpolarization).

(Choice E) The intracellular concentration of mRNA increases during cellular states of elevated protein synthesis (eg, during cell division).

(Choice F) Nitric oxide (NO) is a paracrine signaling molecule with a lifetime of a few seconds. It can freely cross cell membranes and functions as a critical component of endothelium-mediated vasodilation. NO is synthesized from arginine and O_2 by the enzyme NO-synthase.

Educational objective:

The phosphoinositol second messenger system begins with ligand-receptor binding and G_q-protein activation leading to activation of phospholipase C (PLC). PLC then hydrolyzes phosphatidyl inositol bisphosphate and forms diacylglycerol and inositol triphosphate (IP_3). Finally, IP_3 activates protein kinase C via an increase in intracellular Ca^{2+}.

Biochemistry	Biochemistry (General Principles)	Signal transduction
Subject	System	Topic

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A 2-year-old boy is being evaluated for failure to thrive and developmental delay. His past medical history is significant for recurrent ear infections since age 6 months. Physical examination shows coarse facial features, corneal clouding, hepatosplenomegaly, and restricted joint mobility. Mass spectrometry analysis is performed on cultured fibroblasts and reveals deficient phosphorylation of mannose residues on certain glycoproteins in the Golgi apparatus. Normally, these proteins are most likely to be transported to which of the following cellular locations?

A. Extracellular space
B. Lysosome
C. Mitochondria
D. Nucleus
E. Plasma membrane

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A 2-year-old boy is being evaluated for failure to thrive and developmental delay. His past medical history is significant for recurrent ear infections since age 6 months. Physical examination shows coarse facial features, corneal clouding, hepatosplenomegaly, and restricted joint mobility. Mass spectrometry analysis is performed on cultured fibroblasts and reveals deficient phosphorylation of mannose residues on certain glycoproteins in the Golgi apparatus. Normally, these proteins are most likely to be transported to which of the following cellular locations?

- ✗ A. Extracellular space (8%)
- ✓ B. Lysosome (77%)
- C. Mitochondria (2%)
- D. Nucleus (0%)
- E. Plasma membrane (11%)

Incorrect
Correct answer
B

77%
Answered correctly

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This patient has **inclusion cell (I-cell) disease**, an autosomal recessive lysosomal storage disorder. I-cell disease occurs due to defects in **protein targeting**, a process by which proteins are transported to their appropriate intra- or extracellular location. Post-translational modifications (eg, folding, glycosylation, and phosphorylation) often function as markers that help guide the protein to its final destination.

Proteins targeted for **lysosomes** are modified differently than those destined for extracellular secretion. A Golgi body **phosphotransferase enzyme** catalyzes the **phosphorylation of mannose residues** on lysosome-bound proteins, allowing them to traverse the Golgi network and ultimately be transported to the lysosome, where they serve as catalysts for degradation of cellular components.

A defective phosphotransferase enzyme causes extracellular secretion of these proteins and accumulation of cellular debris in the lysosome, forming the characteristic inclusion bodies seen in I-cell disease. Patients with this disorder typically present with failure to thrive and cognitive deficits in the first year of life along with characteristic physical features (eg, coarse facial features, corneal clouding). I-cell disease is typically fatal in childhood.

(Choice A) Following translation in the endoplasmic reticulum, secretory proteins traverse the Golgi apparatus and are packaged into vesicles that ultimately fuse with the plasma membrane, facilitating extracellular protein secretion.

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apparatus and are packaged into vesicles that ultimately fuse with the plasma membrane, facilitating extracellular protein secretion.

(Choice C) Most mitochondrial proteins are synthesized in the cytosol and contain specific mitochondrial targeting sequences. Translocases detect these sequences and shuttle the proteins into and between the different mitochondrial compartments.

(Choice D) In order for nuclear proteins to be imported into the nucleus, they must first present a nuclear localization signal to nuclear pore complexes located on the nuclear envelope. A different nuclear export signal is required for proteins to leave the nucleus.

(Choice E) Peripheral membrane proteins may be modified through a lipidation process in which a hydrophobic lipid anchor is covalently attached to the protein. This process facilitates protein interaction with the cell membrane.

Educational objective:
Protein targeting is the process by which proteins with different intra- and extracellular fates reach their destination. Proteins destined for the lysosome require phosphorylation of specific mannose residues to ensure proper transit through the Golgi apparatus.

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An 11-year-old girl is evaluated for blurry vision. The patient was adopted internationally at age 9. She has no history of head or eye trauma or exposure to ionizing radiation. Motor and cognitive milestones have been achieved at the appropriate age. She has a good appetite and does not follow any specific diet. The patient takes no medications and has no allergies. Vaccinations are up to date. Vital signs are normal. She is at the 40th percentile for height and weight. Other than bilateral lens opacities, the rest of her examination is normal. Urine is positive for reducing substances. Deficient activity of which of the following enzymes is the most likely cause of this patient's eye condition?

A. Aldolase B
B. Alpha-galactosidase A
C. Fructokinase
D. Galactokinase
E. Glucose-6-phosphatase
F. Hexosaminidase A
G. Sphingomyelinase

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been achieved at the appropriate age. She has a good appetite and does not follow any specific diet. The patient takes no medications and has no allergies. Vaccinations are up to date. Vital signs are normal. She is at the 40th percentile for height and weight. Other than bilateral lens opacities, the rest of her examination is normal. Urine is positive for reducing substances. Deficient activity of which of the following enzymes is the most likely cause of this patient's eye condition?

- A. Aldolase B (20%)
- B. Alpha-galactosidase A (6%)
- C. Fructokinase (10%)
- D. Galactokinase (52%)
- E. Glucose-6-phosphatase (2%)
- F. Hexosaminidase A (4%)
- G. Sphingomyelinase (2%)

Incorrect
Correct answer

52%
Answered correctly

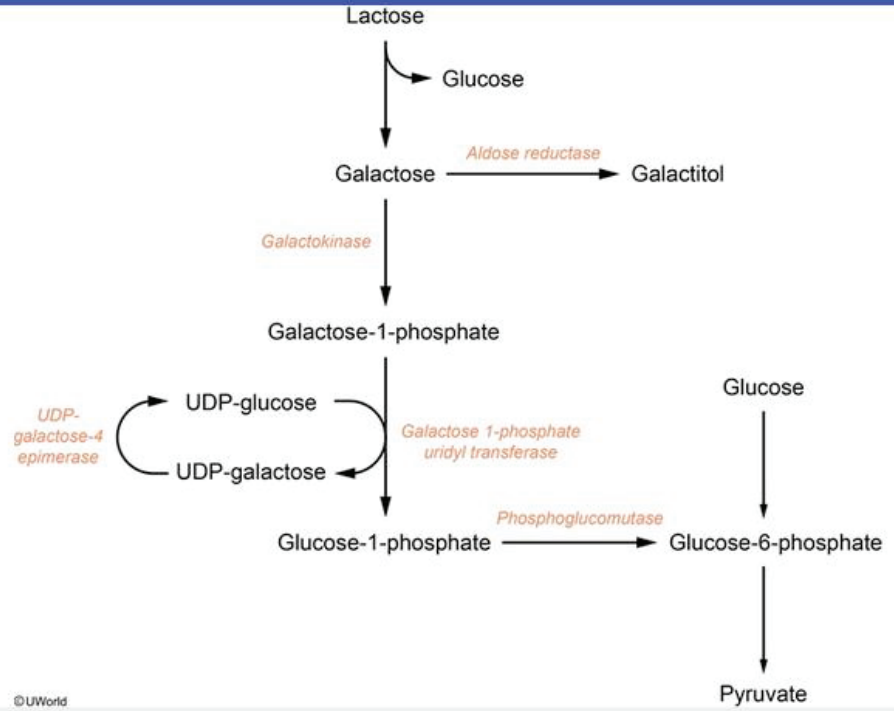
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Galactosemia results from deficiency of enzymes involved in galactose metabolism. First, lactose is broken down to galactose and glucose. Galactose is then phosphorylated to galactose-1-phosphate by the enzyme **galactokinase** (GALK). GALK deficiency causes galactose buildup and this excess is converted to **galactitol**, an osmotic agent that causes **cataracts**. Excess galactose also spills into the urine and causes it to test positive for a reducing substance. Serious systemic manifestations are not seen in GALK deficiency, and cataracts may be the only manifestation.

In contrast, deficiency of the enzyme galactose-1-phosphate uridyl transferase (GALT) results in a more serious form of galactosemia. This is related to the accumulation of galactose-1-phosphate, a toxic metabolite that causes hepatic and renal dysfunction. Consequently, patients with GALT deficiency present early, in the neonatal period, with vomiting, lethargy, and failure to thrive.

This patient's late presentation, normal growth, and the isolated presence of cataract are indicative of GALK deficiency. Infants born in the United States undergo **routine newborn screens** for detecting inborn errors of metabolism, such as galactosemia.

(Choice A) Patients with aldolase B deficiency (hereditary fructose intolerance) cannot metabolize fructose and develop hypoglycemia, hypophosphatemia, and failure to thrive. Although reducing substances can be positive in the urine, cataracts are not present.

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substances can be positive in this urine, cataracts are not present.

(Choice B) Alpha-galactosidase A deficiency (X-linked recessive) results in Fabry disease, which can present with cataracts. However, neurological findings (eg, numbness, tingling, burning pain in the hands and feet) and angiokeratomas are also characteristic.

(Choice C) Fructokinase deficiency leads to essential fructosuria, a benign condition that can result in a positive test for reducing substance but not cataracts.

(Choice E) Glucose-6-phosphatase converts glucose-6-phosphate to glucose. Deficiency of glucose-6-phosphatase causes glycogen storage disease type 1 (von Gierke disease). The main clinical manifestations are hypoglycemia, lactic acidosis, hepatomegaly, and hypertriglyceridemia. Cataracts are not seen.

(Choice F) Tay-Sachs disease results from hexosaminidase A deficiency. Affected infants have retinal cherry-red spots and loss of motor skills. Cataracts are not seen.

(Choice G) Sphingomyelinase deficiency is seen in Niemann-Pick disease and leads to accumulation of sphingomyelin. Characteristics include hepatosplenomegaly, motor neuropathy, anemia, and macular cherry-red spots but not cataracts.

Educational objective:

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substances can be positive in this urine, cataracts are not present.

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Educational objective:

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manifestations are hypoglycemia, lactic acidosis, hepatomegaly, and hypertriglyceridemia. Cataracts are not seen.

(Choice F) Tay-Sachs disease results from hexosaminidase A deficiency. Affected infants have retinal cherry-red spots and loss of motor skills. Cataracts are not seen.

(Choice G) Sphingomyelinase deficiency is seen in Niemann-Pick disease and leads to accumulation of sphingomyelin. Characteristics include hepatosplenomegaly, motor neuropathy, anemia, and macular cherry-red spots but not cataracts.

Educational objective:

Lenticular accumulation of galactitol in the lenses of patients with galactosemia can cause osmotic damage and development of cataracts. Cataracts may be the only manifestation of galactokinase deficiency.

References

- Early cataract formation due to galactokinase deficiency: impact of newborn screening.

Biochemistry	Biochemistry (General Principles)	Galactosemia
Subject	System	Topic

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A 14-month-old boy is evaluated for failure to thrive and developmental delay. His mother reports that at 12 months he could barely lift his head and had difficulty sitting unsupported. The toddler has not started babbling or forming words. He is at the 10th percentile for height and 5th percentile for weight. Laboratory results are as follows:

Hemoglobin	8.6 g/dL
Mean corpuscular volume	114 fL
Reticulocytes	1%
Ammonia, plasma	42 µg/dL normal: 40-80 µg/dL

Urine specimens contain large amounts of orotic acid crystals. Supplementation with which of the following substances would most likely benefit this patient?

A. Ascorbic acid

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Reticulocytes	1%
Ammonia, plasma	42 µg/dL normal: 40-80 µg/dL

Urine specimens contain large amounts of orotic acid crystals. Supplementation with which of the following substances would most likely benefit this patient?

A. Ascorbic acid
B. Folic acid
C. Guanine
D. Iron
E. Pyridoxine
F. Uridine

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Reticulocytes	1%
Ammonia, plasma	42 µg/dL normal: 40-80 µg/dL

Urine specimens contain large amounts of orotic acid crystals. Supplementation with which of the following substances would most likely benefit this patient?

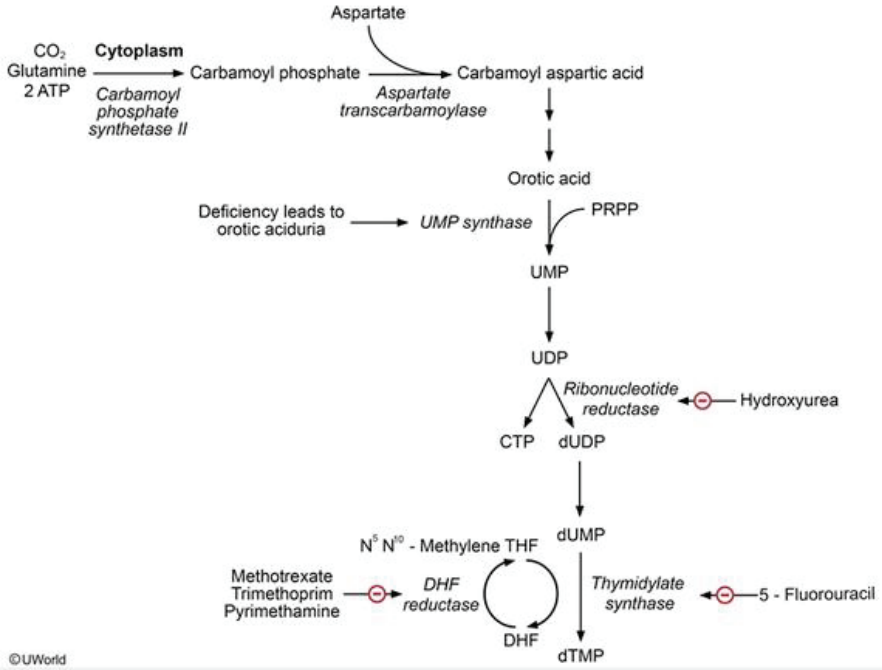
A. Ascorbic acid (2%)
B. Folic acid (26%)
C. Guanine (5%)
D. Iron (1%)
E. Pyridoxine (23%)
✓ F. Uridine (40%)

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De novo pyrimidine synthesis



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dTMP

This patient likely has **hereditary orotic aciduria**, a rare autosomal recessive disorder of de novo pyrimidine synthesis that results in **physical and mental retardation** (eg, low height/weight, delayed developmental milestones), **megaloblastic anemia** (eg, elevated mean corpuscular volume, low reticulocyte count), and **elevated urinary orotic acid** levels. Increased urinary orotic acid may also be seen in ornithine transcarbamylase deficiency; however, patients with this condition classically have failure to thrive and hyperammonemic encephalopathy within the first few weeks of life (due to impaired urea synthesis).

Hereditary orotic aciduria occurs due to a **defect** in **uridine 5'-monophosphate (UMP) synthase**, a polypeptide containing 2 enzymatic domains (orotate phosphoribosyltransferase and OMP decarboxylase) that catalyze the final conversion of orotic acid to UMP. Impaired conversion of orotic acid to UMP results in the excretion of large amounts of orotic acid in the urine and the clinical features described above. **Uridine supplementation** can bypass this enzymatic defect and improve symptoms as uridine is converted to UMP via nucleoside kinases.

(Choice A) Ascorbic acid (vitamin C) is required for hydroxylation of proline and lysine residues in collagen synthesis; therefore, it plays an important role in connective tissue maintenance and wound healing.

(Choice B) Folate participates in single-carbon transfer reactions, as in the de novo synthesis of purines

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(Choice B) Folate participates in single carbon transfer reactions, as in the de novo synthesis of purines and thymidine. Folate supplements will improve megaloblastic anemia resulting from folate deficiency but will not improve the anemia in orotic aciduria.

(Choice C) Guanine and adenine are purine bases present in DNA and RNA. Orotic aciduria is a defect in the synthesis of pyrimidine bases, so supplementation with purines would not affect orate synthesis.

(Choice D) Iron supplementation improves iron deficiency anemia, classically a microcytic hypochromic anemia.

(Choice E) Pyridoxine (vitamin B_6) supplementation is indicated during treatment with isoniazid. Pyridoxine is a cofactor in transamination, deamination, decarboxylation, and condensation reactions.

Educational objective:

Orotic aciduria is a rare autosomal recessive disorder of de novo pyrimidine synthesis that occurs due to a defect in uridine 5'-monophosphate (UMP) synthase. Children typically present with physical and mental retardation, megaloblastic anemia, and large amounts of urinary orotic acid. Uridine supplementation can improve symptoms as uridine is converted to UMP via nucleoside kinases.

References

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A 12-year-old boy is brought to the emergency department with severe chest pain. He has had intermittent substernal chest pain for the past few months that typically occurs after heavy activity. The boy's activities have been limited due to the chest pain, and he is no longer able to play on the soccer team. The patient does not use tobacco or illicit drugs. His temperature is 36.7 C (98 F), blood pressure is 130/80 mm Hg, pulse is 132/min, respirations are 24/min, and pulse oximetry is 98% on room air. BMI is 17 kg/m^2. Physical examination shows an anxious-appearing boy with a rapid but regular pulse. No abnormalities are seen. Troponin is elevated, and ECG reveals ST segment elevations in leads II, III, and aVF. After acute stabilization and treatment, further laboratory workup shows an increased serum methionine level. Which of the following amino acids is most likely essential in this patient?

A. Asparagine
B. Cysteine
C. Isoleucine
D. Leucine
E. Tyrosine

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substernal chest pain for the past few months that typically occurs after heavy activity. The boy's activities have been limited due to the chest pain, and he is no longer able to play on the soccer team. The patient does not use tobacco or illicit drugs. His temperature is 36.7 C (98 F), blood pressure is 130/80 mm Hg, pulse is 132/min, respirations are 24/min, and pulse oximetry is 98% on room air. BMI is 17 kg/m^2. Physical examination shows an anxious-appearing boy with a rapid but regular pulse. No abnormalities are seen. Troponin is elevated, and ECG reveals ST segment elevations in leads II, III, and aVF. After acute stabilization and treatment, further laboratory workup shows an increased serum methionine level. Which of the following amino acids is most likely essential in this patient?

A. Asparagine
B. Cysteine
C. Isoleucine
D. Leucine
E. Tyrosine
F. Valine

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does not use tobacco or illicit drugs. His temperature is 36.7 C (98 F), blood pressure is 130/80 mm Hg, pulse is 132/min, respirations are 24/min, and pulse oximetry is 98% on room air. BMI is 17 kg/m^2.

Physical examination shows an anxious-appearing boy with a rapid but regular pulse. No abnormalities are seen. Troponin is elevated, and ECG reveals ST segment elevations in leads II, III, and aVF. After acute stabilization and treatment, further laboratory workup shows an increased serum methionine level. Which of the following amino acids is most likely essential in this patient?

- A. Asparagine (4%)
- ✓ B. Cysteine (73%)
- C. Isoleucine (1%)
- D. Leucine (3%)
- E. Tyrosine (14%)
- F. Valine (2%)

Correct

73%
Answered correctly

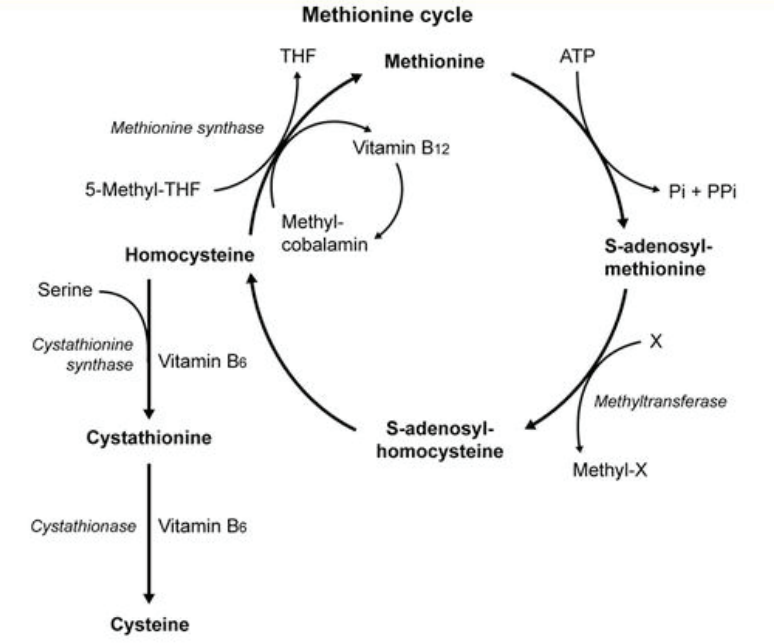
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The amino acid methionine can be metabolized into S-adenosyl-methionine (SAM), which acts as a methyl-donor for many methyltransferase reactions. After the transfer of a methyl group, SAM is converted into S-adenosyl-homocysteine, which is broken down to form adenosine and homocysteine. Subsequently, the conversion of homocysteine to cystathionine requires the enzyme cystathionine synthase, the amino acid serine, and the cofactor vitamin B_6. Cystathionine is then converted to cysteine by the enzyme cystathionase, which also requires vitamin B_6 as a cofactor. Alternatively, the enzyme methionine synthase uses vitamin B_{12} as a cofactor to revert homocysteine back to methionine.

This patient most likely has **homocystinuria**, a condition that leads to **hypercoagulability** and **thromboembolic occlusion**. Because homocysteine is prothrombotic, individuals with complete cystathionine synthase deficiency can develop premature acute coronary syndrome, as seen in this patient (based on his troponin level and ECG findings). Other clinical features include **ectopia lentis** (ocular lens displacement) and **intellectual disability**.

The most common cause of homocystinuria is a defect in **cystathionine synthase**. Affected patients cannot form cysteine from homocysteine; therefore, cysteine is essential in their diet. In addition, homocysteine buildup results in **hypermethioninemia**, as seen in this patient.

(Choice A) The enzyme asparagine synthase converts aspartate to asparagine, the amino acid that is

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(Choice A) The enzyme asparagine synthase converts aspartate to asparagine, the amino acid that is essential for rapidly dividing tumor cells that cannot produce it quickly enough on their own. The chemotherapy drug asparaginase decreases asparagine concentration in tumor cells and leads to lysis of these rapidly growing cells.

(Choices C, D, and F) Maple syrup urine disease is an amino acid disorder caused by deficiency of branched-chain α-ketoacid dehydrogenase. This deficiency leads to toxic buildup of branched-chain amino acids (leucine, isoleucine, and valine) and their metabolites, resulting in feeding difficulties, seizures, cerebral edema, and a sweet odor of the urine.

(Choice E) Phenylalanine hydroxylase catalyzes the hydroxylation of the essential amino acid phenylalanine to form tyrosine. Deficiency of phenylalanine hydroxylase is the most common cause of phenylketonuria, which results in severe intellectual disability if left untreated.

Educational objective:
Homocystinuria is most commonly caused by a defect in cystathionine synthase, resulting in an inability to form cysteine from homocysteine. Cysteine becomes essential in affected patients, and homocysteine buildup leads to elevated methionine. Homocysteine is prothrombotic, resulting in premature thromboembolic events (eg, atherosclerosis, acute coronary syndrome) in these patients.

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A dermatology researcher is studying the role of different amino acids in wound healing. She cultures mature dermal fibroblasts in growth media. After several days, the fibroblasts begin synthesizing polypeptide chains that assemble into triple helical structures, followed by fibrils. The fibrillar proteins are hydrolyzed and separated into their constituent amino acids via paper chromatography. Which of the following amino acids is most likely to be found in highest quantity in these proteins?

A. Alanine
B. Cysteine
C. Glycine
D. Leucine
E. Lysine
F. Proline

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A. Alanine (1%)
B. Cysteine (3%)
C. Glycine (56%)
D. Leucine (2%)
E. Lysine (12%)
F. Proline (24%)

Correct

56%
Answered correctly

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Collagen is the most abundant protein in the human body and is synthesized by fibroblasts, osteoblasts, and chondroblasts. It consists of 3 polypeptide **alpha chains** held together by hydrogen bonds, forming a rope-like **triple helix** (collagen molecule). Collagen molecules self-assemble into fibrils, which subsequently crosslink to form collagen fibers.

The triple helical conformation of collagen molecules occurs due to the simple and repetitive amino acid sequence within each alpha chain, in which **glycine** (Gly) occupies **every third amino acid** position (Gly-X-Y). Glycine is the most abundant amino acid in collagen and, due to its small size, is the only amino acid that can fit into the confined space between individual alpha chains.

(Choices A, B, D, E, and F) None of the other amino acids are as abundant as glycine in collagen. X often represents proline and Y is often hydroxyproline or hydroxylysine. Proline residues are essential for alpha helix formation because their ring configuration introduces a kink in the polypeptide chain, enhancing the rigidity of the helical structure. Hydroxylysine is necessary for cross-linking, which greatly increases the tensile strength of assembled collagen fibers.

Educational objective:
Glycine is the most abundant amino acid in collagen. The triple helical conformation of collagen molecules occurs due to the repetitive amino acid sequence within each alpha chain, in which glycine (Gly) occupies

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The triple helical conformation of collagen molecules occurs due to the simple and repetitive amino acid sequence within each alpha chain, in which **glycine** (Gly) occupies **every third amino acid** position (Gly-X-Y). Glycine is the most abundant amino acid in collagen and, due to its small size, is the only amino acid that can fit into the confined space between individual alpha chains.

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Educational objective:

Glycine is the most abundant amino acid in collagen. The triple helical conformation of collagen molecules occurs due to the repetitive amino acid sequence within each alpha chain, in which glycine (Gly) occupies every third amino acid position (Gly-X-Y).

References

- Collagen structure and stability.

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www.ncbi.nlm.nih.gov/pubmed/19344236

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A 54-year-old woman is evaluated for progressive constipation, anorexia, and a 5.4-kg (12-lb) weight loss over the past several months. Physical examination is unremarkable. Stool guaiac test is positive, and a colonoscopy is performed. An exophytic mass is identified in the sigmoid colon. The patient undergoes a left hemicolectomy, and histopathology of the surgical specimen is positive for adenocarcinoma. Molecular testing of the cancer cells reveals a mutation in the *KRAS* gene that results in constitutive activation of the Ras protein. Under normal circumstances, this protein is only active when bound to which of the following substances?

A. ATP
B. Ca^{2+}
C. cAMP
D. GTP
E. IP_3

Submit

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A 54-year-old woman is evaluated for progressive constipation, anorexia, and a 5.4-kg (12-lb) weight loss over the past several months. Physical examination is unremarkable. Stool guaiac test is positive, and a colonoscopy is performed. An exophytic mass is identified in the sigmoid colon. The patient undergoes a left hemicolectomy, and histopathology of the surgical specimen is positive for adenocarcinoma. Molecular testing of the cancer cells reveals a mutation in the *KRAS* gene that results in constitutive activation of the Ras protein. Under normal circumstances, this protein is only active when bound to which of the following substances?

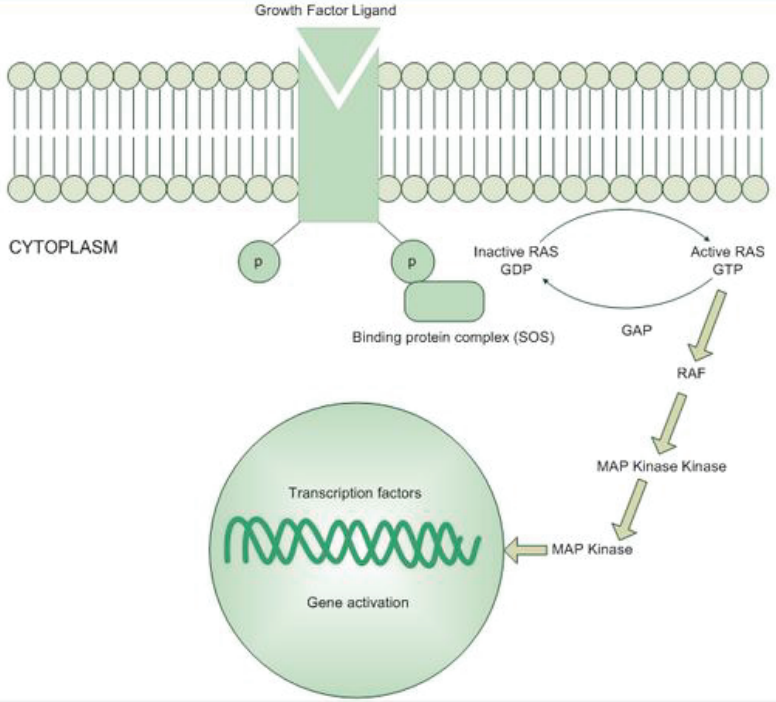
- A. ATP (13%)
- B. Ca^{2+} (7%)
- C. cAMP (15%)
- ✓ D. GTP (55%)
- E. IP_3 (8%)

55% 02 mins, 10 secs 09/22/2020

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RAS genes code for a family of small G-proteins involved in signal transduction in the Ras-MAPK pathway. Ras proteins exist in 2 different states: an **inactive GDP-bound state** and an **active GTP-bound state**. Ras becomes activated when a growth factor ligand binds to a **receptor tyrosine kinase** located on the cell membrane, causing autophosphorylation of the receptor. This triggers binding of adaptor proteins that interact with Ras, promoting GDP removal and GTP binding. Activated Ras then begins a phosphorylation cascade that results in the activation of **mitogen-activated protein kinase (MAPK)**, which enters the nucleus to influence gene transcription.

Ras proteins have intrinsic GTPase activity that allows them to hydrolyze GTP; this mechanism prevents accumulation of active Ras (GTP-bound) in the absence of hormonal signaling. *RAS* gene mutations can lead to decreased intrinsic GTPase activity; this results in a constitutively activated Ras protein that causes constant and unregulated cell proliferation. *RAS* mutations are commonly identified in cancerous tumors, specifically colorectal and pancreatic malignancies.

(Choices A and C) ATP serves as a phosphate source for kinase-dependent phosphorylation reactions involved in numerous intracellular signaling pathways. It is also used as a substrate to produce cyclic AMP (cAMP) in the cAMP second messenger system.

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(Choice B) Ca^{2+} is important for cell signaling as its intracellular presence alters the function of many proteins and enzymes. Ca^{2+} is required for many basic physiologic activities including apoptosis, muscular contraction, and neuronal transmission.

(Choice E) IP_3 is the water-soluble component of the IP_3/DAG second messenger system. IP_3 acts on the endoplasmic reticulum to cause intracellular Ca^{2+} release while DAG remains in the cell membrane and activates membrane-bound protein kinases.

Educational objective:

Regulation of the Ras-MAPK signal transduction pathway requires a balance between active (GTP-bound) and inactive (GDP-bound) Ras proteins. *RAS* gene mutations, which result in constitutively activated Ras proteins, are implicated in the development of malignant tumors.

References

- MEK inhibitors: a therapeutic approach to targeting the Ras-MAP kinase pathway in tumors.

Biochemistry	Biochemistry (General Principles)	Colorectal polyps and cancer
Subject	System	Topic

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A 31-year-old man comes to the office for a routine checkup. He has no significant medical problems and does not take any medications. The patient works as a fitness trainer and lifts weights recreationally. He has been consuming carbohydrate-rich food prior to his weightlifting sessions and claims that it increases muscle strength. A literature review shows that the rate of glycogenolysis within myocytes increases several hundredfold during active skeletal muscle contraction. Which of the following substances is most likely responsible for increasing the reaction rate during active contraction?

A. ATP
B. Ca^{2+}
C. cAMP
D. Glucose-6-phosphate
E. Lactate

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A 31-year-old man comes to the office for a routine checkup. He has no significant medical problems and does not take any medications. The patient works as a fitness trainer and lifts weights recreationally. He has been consuming carbohydrate-rich food prior to his weightlifting sessions and claims that it increases muscle strength. A literature review shows that the rate of glycogenolysis within myocytes increases several hundredfold during active skeletal muscle contraction. Which of the following substances is most likely responsible for increasing the reaction rate during active contraction?

- A. ATP (15%)
- ✓ B. Ca^{2+} (38%)
- C. cAMP (22%)
- D. Glucose-6-phosphate (6%)
- E. Lactate (16%)

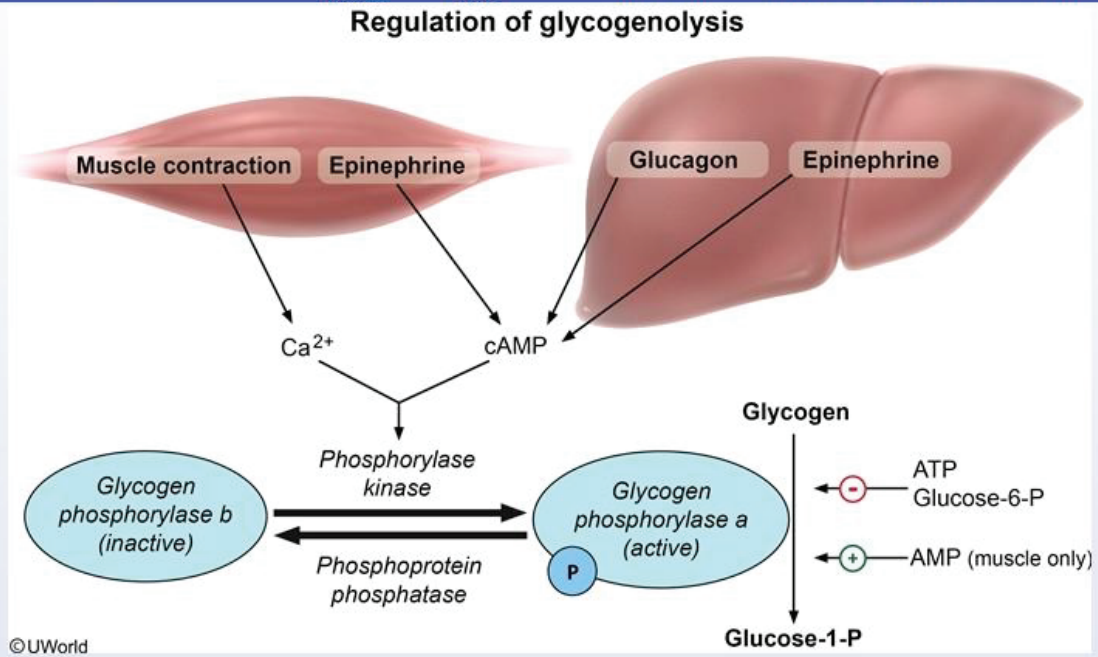
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38% Answered correctly

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Glycogen is broken down by the enzyme **glycogen phosphorylase**, which is regulated through phosphorylation (active state) and dephosphorylation (inactive state). **Phosphorylase kinase (PK)** is the enzyme responsible for the phosphorylation of glycogen phosphorylase, whereas **phosphoprotein phosphatase** catalyzes its dephosphorylation.

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phosphatase catalyzes its dephosphorylation.

PK is regulated differently in liver than in muscles. Glycogen stored in the **liver** is used to maintain blood glucose levels during the fasting state, whereas glycogen in the muscles is used to provide energy for muscle contraction. In the liver, PK is activated primarily through the binding of **epinephrine and glucagon** to G_s protein-coupled receptors, which **increases cAMP concentrations** and causes phosphorylation of PK (via protein kinase A).

Skeletal muscle lacks glucagon receptors, but muscle PK can still be phosphorylated in response to an epinephrine-induced increase in cAMP concentrations. However, increased **intracellular calcium** is a more powerful activator of muscle PK. Release of sarcoplasmic calcium stores following neuromuscular acetylcholine stimulation allows for **synchronization** of skeletal muscle contraction and glycogen breakdown, providing the energy necessary for anaerobic muscle contraction.

(Choices A and D) Phosphorylated glycogen phosphorylase (active form) is allosterically inhibited by ATP and glucose-6-phosphate in both liver and muscle cells. Increased intracellular ATP levels help to decrease the rate of glycogenolysis upon cessation of active muscle contraction.

(Choice C) Although increased cAMP stimulates muscle glycogen breakdown via the action of epinephrine on beta-1 adrenergic receptors, it is not responsible for synchronization of active muscle

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decrease the rate of glycogenolysis upon cessation of active muscle contraction.

(Choice C) Although increased cAMP stimulates muscle glycogen breakdown via the action of epinephrine on beta-1 adrenergic receptors, it is not responsible for synchronization of active muscle contraction and glycogen breakdown.

(Choice E) Lactate is produced in tissues during anaerobic glycolysis, such as in muscles during strenuous exercise as a result of relatively hypoxic conditions. The lactate produced by the muscles can be converted to glucose in the liver via gluconeogenesis.

Educational objective:

Synchronization of glycogen degradation with skeletal muscle contraction occurs due to release of sarcoplasmic calcium following neuromuscular stimulation. Increased intracellular calcium causes activation of phosphorylase kinase, stimulating glycogen phosphorylase to increase glycogenolysis.

References

- Muscle glycogenolysis. Regulation of the cyclic interconversion of phosphorylase a and phosphorylase b.

Biochemistry	Biochemistry (General Principles)	Physical exercise
Subject	System	Topic

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As part of a research study investigating enzymatic activity in both normal and diseased liver tissue, hepatocytes are isolated from biopsy samples obtained from patients undergoing routine care at a local tertiary referral center. The cells are homogenized and centrifuged to remove membrane components and organelles. Following subsequent rounds of centrifugation, the remaining supernatant contains only cytosol and cytosolic proteins. Activity of which of the following enzymes will most likely be detectable in the supernatant of healthy liver cells?

A. 3-Hydroxy-3-methylglutaryl-CoA lyase
B. Ornithine transcarbamylase
C. Pyruvate carboxylase
D. Succinate dehydrogenase
E. Transketolase

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As part of a research study investigating enzymatic activity in both normal and diseased liver tissue, hepatocytes are isolated from biopsy samples obtained from patients undergoing routine care at a local tertiary referral center. The cells are homogenized and centrifuged to remove membrane components and organelles. Following subsequent rounds of centrifugation, the remaining supernatant contains only cytosol and cytosolic proteins. Activity of which of the following enzymes will most likely be detectable in the supernatant of healthy liver cells?

A. 3-Hydroxy-3-methylglutaryl-CoA lyase (10%)
B. Ornithine transcarbamylase (18%)
C. Pyruvate carboxylase (26%)
D. Succinate dehydrogenase (6%)
E. Transketolase (37%)

Incorrect
Correct answer
E

37%
Answered correctly

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Enzymes and the biochemical processes they catalyze often require distinct chemical environments for optimal function; small variations in temperature, molecular concentrations, and pH may render them ineffective. **Cellular compartmentalization** provides a means by which multiple heterogeneous environments can exist within a cell. Organelles such as the nucleus and mitochondria form distinct, membrane-bound regions with a chemical composition different from the cytosol. This allows multiple biochemical processes to occur simultaneously at maximum efficiency.

The cytosol and mitochondria are the predominant sites of metabolism in the cell. Mitochondria are the site of beta-oxidation of fatty acids, the citric acid cycle, and the carboxylation of pyruvate (gluconeogenesis). The **cytosol** is home to enzymes necessary for glycolysis, fatty acid synthesis, and the **pentose phosphate pathway**. **Transketolase** is an enzyme of the pentose phosphate pathway that uses thiamine (vitamin B_1) as a cofactor to shuttle 2-carbon fragments between sugar molecules. Other processes such as heme synthesis, the urea cycle, and gluconeogenesis rely on a complex interplay between the mitochondria and cytosol to function optimally; enzymes present in both cellular compartments are required for these metabolic pathways.

(Choice A) 3-Hydroxy-3-methylglutaryl-CoA (HMG CoA) lyase is a mitochondrial enzyme necessary for ketogenesis. It is also responsible for metabolism of the ketogenic amino acid, leucine.

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(Choice A) 3-Hydroxy-3-methylglutaryl-CoA (HMG CoA) lyase is a mitochondrial enzyme necessary for ketogenesis. It is also responsible for metabolism of the ketogenic amino acid, leucine.

(Choice B) Ornithine transcarbamylase catalyzes the combination of ornithine and carbamoyl phosphate to form citrulline in the urea cycle. This reaction occurs within the mitochondria.

(Choice C) Pyruvate carboxylase catalyzes the initial step in gluconeogenesis by converting pyruvate to oxaloacetate. This enzyme requires biotin as a cofactor, and functions within the mitochondria.

(Choice D) Succinate dehydrogenase is a TCA cycle enzyme that converts succinate to fumarate. It is an inner mitochondrial membrane protein and functions as part of the electron transport chain.

Educational objective:
Cellular compartmentalization allows multiple biochemical processes to occur simultaneously at maximum efficiency. Beta-oxidation of fatty acids, the TCA cycle, and the carboxylation of pyruvate (gluconeogenesis) all occur within the mitochondria. The enzymes responsible for glycolysis, fatty acid synthesis, and the pentose phosphate pathway reside in the cytosol.

Biochemistry	Biochemistry (General Principles)	Principles of cell biology
Subject	System	Topic

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Nutrition researchers investigating the relationship between fructose consumption and cardiovascular disease conduct a prospective cohort study on a population of randomly selected young adults. Study participants undergo semiannual measurement of waist circumference, blood pressure, and serum cholesterol and triglyceride concentrations. Dietary fructose consumption is assessed through the use of questionnaires and by measuring urinary fructose excretion. A 23-year-old man enrolled in the study is found to excrete large amounts of fructose in his urine compared to other study participants despite maintaining a moderate fructose intake. Further evaluation shows a hereditary defect in fructose metabolism, but he is asymptomatic and has no other medical problems. This patient most likely remains able to metabolize fructose due to the compensatory activity of which of the following enzymes?

A. Aldolase B
B. Aldose reductase
C. Fructokinase
D. Hexokinase
E. UDP-galactose-4-epimerase

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disease conduct a prospective cohort study on a population of randomly selected young adults. Study participants undergo semiannual measurement of waist circumference, blood pressure, and serum cholesterol and triglyceride concentrations. Dietary fructose consumption is assessed through the use of questionnaires and by measuring urinary fructose excretion. A 23-year-old man enrolled in the study is found to excrete large amounts of fructose in his urine compared to other study participants despite maintaining a moderate fructose intake. Further evaluation shows a hereditary defect in fructose metabolism, but he is asymptomatic and has no other medical problems. This patient most likely remains able to metabolize fructose due to the compensatory activity of which of the following enzymes?

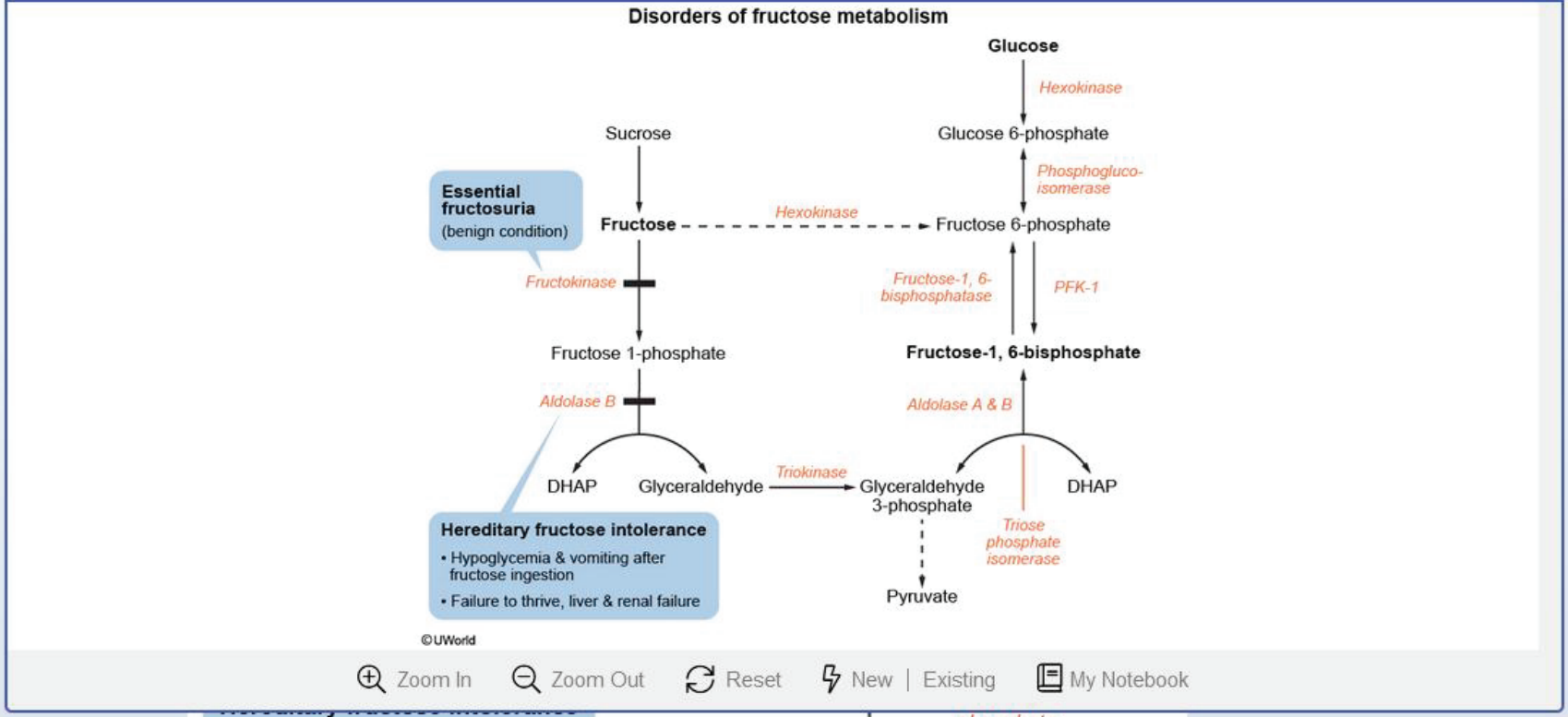
A. Aldolase B (28%)
B. Aldose reductase (15%)
C. Fructokinase (21%)
D. Hexokinase (30%)
E. UDP-galactose-4-epimerase (4%)

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Fructose is obtained in the diet primarily from fruits and food sweeteners such as table sugar (sucrose) and high-fructose corn syrup. Fructose is absorbed in the proximal intestine through the GLUT5 fructose transporter. It is normally phosphorylated by **fructokinase** in the liver, yielding **fructose-1-phosphate**, which is converted by aldolase B to dihydroxyacetone phosphate (DHAP) and glyceraldehyde **(Choice C)**. Glyceraldehyde and DHAP can be converted to glyceraldehyde-3-phosphate, which can then be metabolized in the glycolytic pathway.

Fructokinase deficiency (essential fructosuria) is an **asymptomatic**, autosomal recessive disorder that causes dietary fructose to be excreted unchanged in the urine. In fructokinase deficiency, **hexokinase** takes over the role of fructose metabolism, converting dietary fructose into **fructose-6-phosphate**. Fructose-6-phosphate can be metabolized in the glycolytic pathway or converted to glucose-6-phosphate or glucose-1-phosphate, which can be used in the pentose phosphate pathway or for glycogen synthesis, respectively.

(Choice A) Aldolase B plays a nonessential role in glycolysis due to the redundant function of aldolase A. However, it is particularly important during fructose metabolism as deficiency of this enzyme leads to toxic accumulation of fructose-1-phosphate (hereditary fructose intolerance). This life-threatening disorder presents in infancy after the introduction of fructose-containing foods.

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accumulation of fructose-1-phosphate (hereditary fructose intolerance). This life-threatening disorder presents in infancy after the introduction of fructose-containing foods.

(Choice B) Aldose reductase is the enzyme that converts glucose to sorbitol. Aldose reductase has a low affinity for glucose, and normally only very small amounts of glucose are metabolized by this enzyme. The amount of glucose metabolized by the aldose reductase pathway increases significantly in diabetes mellitus and contributes to chronic complications such as neuropathy and retinopathy.

(Choice E) UDP-galactose-4-epimerase is involved in the metabolism of galactose; it does not play a role in fructose metabolism.

Educational objective:
Essential fructosuria is a benign disorder of fructose metabolism caused by fructokinase deficiency. In patients with essential fructosuria, some of the dietary fructose load is converted by hexokinase to fructose-6-phosphate, which can then enter glycolysis; this pathway is not significant in normal individuals.

Biochemistry	Biochemistry (General Principles)	Fructose metabolism
Subject	System	Topic

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A 24-year-old woman comes to the office for a preemployment medical evaluation. The patient has no known medical problems but reports that her skin bruises and scars easily. She says that most of her family members have a very "flexible" body, and her brother works in a circus as a contortionist. The patient takes no medications and has no allergies. She does not use tobacco, alcohol, or drugs. Physical examination findings are shown in the exhibit. This patient most likely has an inherited defect in which of the following proteins?

A. Collagen
B. Elastin
C. Fibrillin-1
D. Hyaluronic acid
E. Laminin
F. Proteoglycan

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Exhibit 1 Exhibit 2



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A 24-year-old woman comes to the office for a preemployment medical evaluation. The patient has no known medical problems but reports that her skin bruises and scars easily. She says that most of her family members have a very "flexible" body, and her brother works in a circus as a contortionist. The patient takes no medications and has no allergies. She does not use tobacco, alcohol, or drugs. Physical examination findings are shown in the exhibit. This patient most likely has an inherited defect in which of the following proteins?

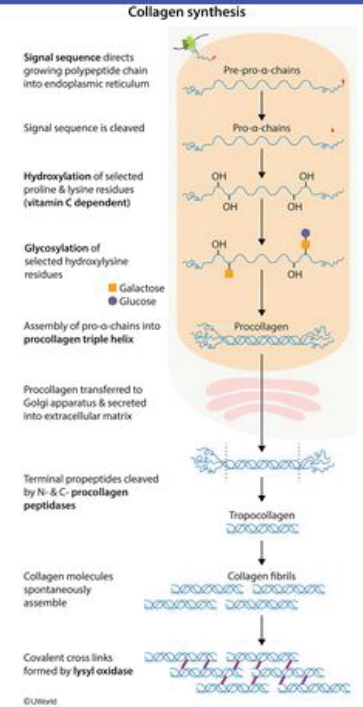
- A. Collagen (76%)
- B. Elastin (14%)
- C. Fibrillin-1 (8%)
- D. ~~Hyaluronic acid~~ (0%)
- E. ~~Laminin~~ (0%)
- F. ~~Proteoglycan~~ (0%)

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Exhibit Display



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The extracellular matrix is a network of interstitial proteins that maintain normal tissue architecture. **Collagen** is a major component of **connective tissue** and consists of 3 polypeptide α chains held together by **hydrogen bonds** to form a ropelike triple helix structure (tropocollagen). **Lysyl oxidase** then forms covalent bonds between individual tropocollagen molecules, generating mature collagen fibers. The variation in amino acid sequences in the collagen α chains gives rise to collagen diversity in different tissues. Collagen types I, II, III, and V provide **tensile strength** in skin, bones, cartilage, tendons, and blood vessels.

Ehlers-Danlos syndrome (EDS) is a group of hereditary disorders involving a defect in collagen synthesis. EDS usually manifests clinically as **hypermobile joints**, **overelastic skin**, and fragile tissue susceptible to bruising, wounds, and hemarthrosis. Common mutations leading to EDS phenotypes include deficiencies of the lysyl hydroxylase and procollagen peptidase enzymes responsible for collagen synthesis.

(Choice B) Elastin, a fibrous protein in the connective tissue, is named for the elastic properties it imparts to skin, blood vessels, and lung alveoli. Elastin fibers can be stretched to several times their original length but will recoil when the stretching forces are withdrawn. Elastin is synthesized from the polypeptide

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(Choice C) Fibrillin-1 is a major component of the microfibrils that form a sheath around elastin. Microfibrils are abundantly present in blood vessels and in the suspensory ligaments of the lens. Defects in the *fibrillin-1* gene cause classic autosomal dominant Marfan syndrome.

(Choice D) Hyaluronic acid is another major component of the soft tissue's extracellular matrix, including synovial fluid and skin. Exogenous injection can be used to restore viscoelasticity to the synovial fluid in osteoarthritis; soft-tissue fillers can also be used in patients concerned about age-related volume loss (eg, nasolabial folds).

(Choice E) Laminins are heterotrimeric glycoproteins that bind to type IV collagen underlying epithelial cells. They contribute to the organization and function of the basal lamina (basement membrane).

(Choice F) Proteoglycans are composed of glycosaminoglycans (GAGs), which provide compressibility to tissues. Patients with deficiencies in lysosomal enzymes cannot break down GAGs, resulting in mucopolysaccharidoses (eg, Hurler syndrome, Hunter syndrome) characterized by soft tissue and skeletal

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Educational objective:
Ehlers-Danlos syndrome (EDS) is a heritable connective tissue disease associated with abnormal collagen formation. EDS usually manifests clinically as overflexible (hypermobile) joints, overelastic (hyperelastic) skin, and fragile tissue susceptible to bruising, wounding, and hemarthrosis.

References

- Clinical and genetic aspects of Ehlers-Danlos syndrome, classic type.

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A 64-year-old man comes to the emergency department due to severe abdominal pain, nausea, and vomiting. He has a history of hypertension, myocardial infarction, and systolic heart failure. His blood pressure is 100/60 mm Hg, pulse is 116/min and irregular, and respirations are 24/min. Examination shows a soft, mildly distended, and tender abdomen. Laboratory results are as follows:

Serum chemistry

Sodium	136 mEq/L
Chloride	96 mEq/L
Bicarbonate	12 mEq/L

Arterial blood gases

pH	7.20
	26 mm

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	mEq/L	
Bicarbonate	12 mEq/L	

Arterial blood gases

pH	7.20	
$PaCO_2$	26 mm Hg	
Lactic acid	6.2 mmol/L	(normal: 0.5-2.2 mmol/L)

CT scan of the abdomen reveals distal ileal wall thickening and lack of enhancement with intravenous contrast. Decreased activity of which of the following enzymes best explains the acid-base disorder in this patient?

A. Enolase

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Lactic acid	6.2 mmol/L	(normal: 0.5-2.2 mmol/L)

CT scan of the abdomen reveals distal ileal wall thickening and lack of enhancement with intravenous contrast. Decreased activity of which of the following enzymes best explains the acid-base disorder in this patient?

A. Enolase
B. Lactate dehydrogenase
C. Pyruvate carboxylase
D. Pyruvate dehydrogenase
E. Pyruvate kinase

Submit

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Lactic acid	6.2 mmol/L	(normal: 0.5-2.2 mmol/L)

CT scan of the abdomen reveals distal ileal wall thickening and lack of enhancement with intravenous contrast. Decreased activity of which of the following enzymes best explains the acid-base disorder in this patient?

A. Enolase (1%)
B. Lactate dehydrogenase (25%)
C. Pyruvate carboxylase (8%)
D. Pyruvate dehydrogenase (57%)
E. Pyruvate kinase (7%)

Correct

57%

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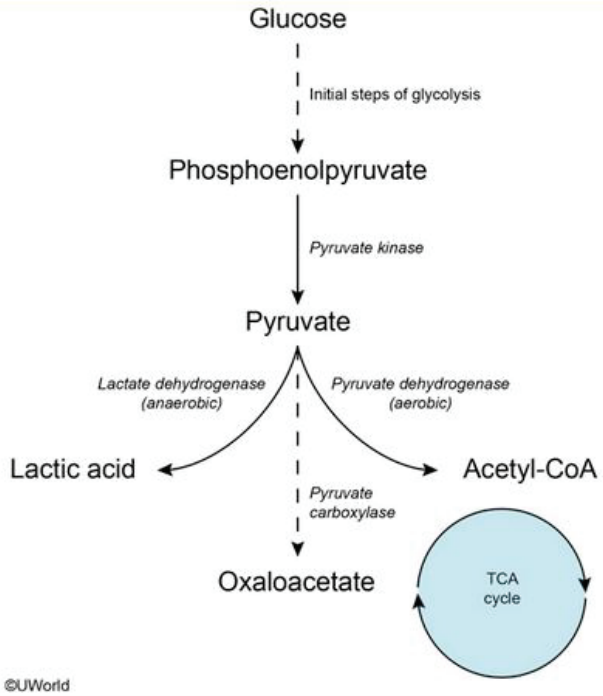
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This patient has **acute mesenteric ischemia**, with inadequate delivery of oxygen to intestinal tissues. During glycolysis, the concentration of oxygen in the tissues affects the metabolic fate of pyruvate. In the presence of oxygen, pyruvate is preferentially converted to acetyl coenzyme A by pyruvate dehydrogenase in the mitochondrial matrix. Acetyl coenzyme A then undergoes oxidation in the citric acid (TCA) cycle. However, under **hypoxic conditions**, intracellular accumulation of NADH **inhibits pyruvate dehydrogenase**. As a result, increased amounts of **pyruvate** are converted to **lactate** by lactate dehydrogenase **(Choice B)**, which regenerates NAD^+ from NADH (allowing for limited ATP production via anaerobic glycolysis). With significant tissue ischemia, lactate begins to accumulate in the circulation and can lead to **lactic acidosis**. Patients with lactic (or other metabolic) acidosis will typically hyperventilate to eliminate CO_2 and induce a compensatory respiratory alkalosis.

(Choices A and E) 2-phosphoglycerate is converted to phosphoenolpyruvate by the enzyme enolase. Phosphoenolpyruvate is subsequently metabolized to pyruvate by pyruvate kinase. These reactions are performed under both aerobic and anaerobic conditions.

(Choice C) Pyruvate can also be converted to oxaloacetate by pyruvate carboxylase. This enzyme is involved in regeneration of glucose from pyruvate by the process of gluconeogenesis.

Educational objective:

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Educational objective:

In the presence of oxygen, pyruvate produced during glycolysis is converted by pyruvate dehydrogenase to acetyl coenzyme A, which is subsequently metabolized by oxidative phosphorylation. However, if inadequate oxygen is present in the tissues, pyruvate is converted to lactate by lactate dehydrogenase, leading to lactic acidosis.

References

- Clinical factors and outcomes in patients with acute mesenteric ischemia in the emergency department.

Biochemistry Biochemistry (General Principles) Metabolic acidosis

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An autopsy is being performed on a 4-year-old boy who recently died from a myocardial infarction. The child had a history of intellectual disability. Autopsy shows a prominent forehead and broad nose. There is a diffuse haze over the corneas bilaterally. The heart, liver, and spleen are enlarged. Sampling of the coronary arteries is most likely to reveal intimal accumulation of which of the following substances?

A. Cholesterol
B. Glucocerebroside
C. Glycogen
D. Heparan sulfate
E. Sphingomyelin

Submit

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An autopsy is being performed on a 4-year-old boy who recently died from a myocardial infarction. The child had a history of intellectual disability. Autopsy shows a prominent forehead and broad nose. There is a diffuse haze over the corneas bilaterally. The heart, liver, and spleen are enlarged. Sampling of the coronary arteries is most likely to reveal intimal accumulation of which of the following substances?

A. ~~Cholesterol~~ (0%)
B. Glucocerebroside (0%)
C. ~~Glycogen~~ (0%)
✓ D. Heparan sulfate (100%)
E. Sphingomyelin (0%)

Correct
Collecting Statistics
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Time Spent
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Last Updated

Explanation

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Mucopolysaccharidoses				
Diagnosis	**Inheritance**	**Deficiency**	**Accumulated substrate**	**Key features**
Hurler syndrome	AR	α-L-iduronidase	Dermatan & heparan sulfate	• Severe developmental delay & intellectual disability • Coarse facial features • Corneal clouding • Hepatosplenomegaly • Death at age <10 (cardiac complications)
Hunter syndrome	XLR	Iduronate sulfatase		• Milder features than Hurler: ◦ (+) Aggressive behavior ◦ (−) Corneal clouding • Death in adolescence/early adulthood

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This patient most likely had **Hurler syndrome** (type I mucopolysaccharidosis), an autosomal recessive disorder characterized by severe **intellectual disability**, **corneal clouding**, and **coarse facial features** (eg, frontal bossing, broad nose, flat midface). Hepatosplenomegaly and heart disease are also typical findings.

Mucopolysaccharidoses are lysosomal storage disorders resulting from the **defective metabolism of glycosaminoglycans** (GAGs). GAGs are long, unbranched polysaccharides that are an important component of the ground substance within the extracellular matrix of connective tissues. Hurler syndrome is caused by a **deficiency** of **alpha-L-iduronidase**, which hydrolyzes dermatan and heparan sulfate. Hunter syndrome, a less severe disease than Hurler syndrome, also results in an accumulation of dermatan and heparan sulfate but characteristically does not cause corneal clouding.

Patients with Hurler syndrome have a shortened life expectancy. Death, typically in early childhood, is usually caused by **cardiac complications** (eg, myocardial infarction); this child's death from coronary artery disease was likely due to **deposition of dermatan and heparan sulfate** within the vessels.

(Choice A) Premature coronary artery disease is seen with familial hypercholesterolemia. Cholesterol deposits can lead to tendon xanthomas, xanthelasmas (ie, eyelid plaques), and/or corneal arcus (ie, gray ring around the cornea) but not coarse facial features, intellectual disability, or a diffuse corneal haze.

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deposits can lead to tendon xanthomas, xanthelasmas (ie, eyelid plaques), and/or corneal arcus (ie, gray ring around the cornea) but not coarse facial features, intellectual disability, or a diffuse corneal haze.

(Choice B) Accumulation of glucocerebroside within mononuclear cells is seen in Gaucher disease, an autosomal recessive defect in beta-glucocerebrosidase. This condition is characterized by bruising due to thrombocytopenia, hepatosplenomegaly, progressive neurologic deterioration, and severe bone pain. Premature coronary artery disease does not occur.

(Choice C) Glycogen storage diseases cause defective metabolism of glycogen in the liver and/or muscles. The presentation can include hypoglycemia, lactic acidosis, hepatomegaly, growth retardation, and/or muscle fatigue/cramping. Cardiomegaly can occur with Pompe disease, but corneal clouding is not a feature.

(Choice E) Niemann-Pick disease results from a deficiency of sphingomyelinase, which leads to the accumulation of sphingomyelin within phagocytes. This disease is characterized by hepatosplenomegaly and progressive neurologic deterioration, but eye findings include a cherry-red spot on the macula, not corneal clouding.

Educational objective:

Hurler syndrome is a mucopolysaccharidosis caused by a deficiency of alpha-L-iduronidase, which

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Premature coronary artery disease does not occur.

(Choice C) Glycogen storage diseases cause defective metabolism of glycogen in the liver and/or muscles. The presentation can include hypoglycemia, lactic acidosis, hepatomegaly, growth retardation, and/or muscle fatigue/cramping. Cardiomegaly can occur with Pompe disease, but corneal clouding is not a feature.

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Educational objective:
Hurler syndrome is a mucopolysaccharidosis caused by a deficiency of alpha-L-iduronidase, which hydrolyzes dermatan and heparan sulfate. Accumulation of these substances results in the characteristic features of intellectual disability, coarse facial features, corneal clouding, and hepatosplenomegaly. Early death due to cardiac complications (eg, myocardial infarction) is expected.

References

- Early disease progression of Hurler syndrome.

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